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# ACNR

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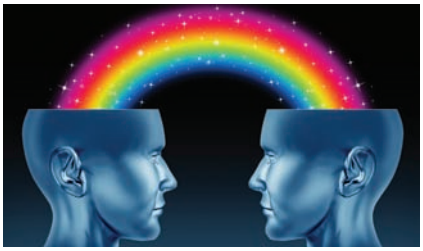
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

## In this issue

# Upcoming meetings for Neurologists from the Royal Society of Medicine

The Royal Society of Medicine hosts over 400 medical events a year covering all areas of medicine. Upcoming meetings useful to neurologists are taking place across the country and all are CPD accredited. For more information see below or visit our website.

## UPCOMING MEETINGS

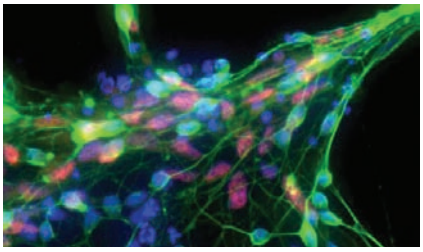


**CNS Series: Treating dementia**
Thursday 30 April 2015 - Royal Society of Medicine, LONDON

The aim of this meeting is to improve diagnostic and management skills in the care of people with dementia. Participants will have improved their ability to differentiate the causes of cognitive dysfunction, and understand the types of dementia. This meeting will cover the future developments in treatment and how health care professionals can work together to improve quality of life for people with dementia and their carers.

**Autism over the lifespan - current thinking**
Thursday 23 April 2015 - Exeter Conference Centre, DEVON

This day meeting, in association with Research Autism, will provide context for the understanding and needs of adolescents and adults with Autistic Spectrum Conditions (ASC) and an opportunity to hear from and ask questions of some of the world's experts in autism. Lectures will include updates from the Avon Longitudinal Study of Parents and Children (ALSPAC).



**Recent studies and the diagnosis of MND**
Wednesday 6 May 2015 - The Foresight Centre, LIVERPOOL

This day meeting, organised by the Royal Society of Medicine and the Motor Neurone Disease Association, will bring together top neurologists and MND Specialists to explore recent studies looking into the diagnosis and early treatment of MND. Delegates will gain a better understanding of the key factors to recognise the early stages of MND vital to improving the quality of life and extending life expectancy in patients.

**Psychiatry and society: Will neuroscience change understandings and practices?**
Tuesday 12 May 2015 - Royal Society of Medicine, LONDON

This high class/low fee conference offers an exceptional opportunity to listen to and interact with an international field of world leaders from neuroscience and social science. Will our understanding of mental health and illness, personal responsibility and psychiatric education change radically? What will be impact on society's expectations of mental health services and the practice of psychiatry?

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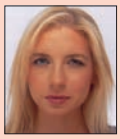

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*Mike Zandi, Editor.*

In this issue Sunaina Yadav, Colombo and Pankaj Sharma, Imperial College, write an excellent review article on the genetics of ischaemic stroke, from CADASIL to common variants that influence ischaemic stroke risk in the general population. This article is introduced further by David Werring on page 6, who is staying on as a Stroke Editor for ACNR to continue the thread of stroke related content.

Irene Sambri and Alessandro Fraldi, Naples write a comprehensive and up-to-date review of lysosomal dysfunction in neurodegenerative diseases, providing an update on autophagy and newly discovered disease mechanisms, including α-synuclein accumulation.

In our rehabilitation article, neuropsychologist Daniel Friedland, Hertfordshire, writes the obituary of the post-concussion syndrome. He discusses the problems of attributing symptoms after mild head injury, the problems of disease classification, not only those experienced in research, due to the DSM5 revisions which have abandoned the entity, but also those clinically. We are encouraged to abandon using the term post-concussion syndrome, and to instead examine symptoms after mild brain injuries, including identifying and treating post-traumatic stress disorder.

In our historical article, Andrew Larner provides a reappraisal of the coverage of cognitive disorders in the Manual of Diseases of the Nervous System of William Gowers, who died a hundred years ago this year.

Geraint Fuller introduces this years ABN meeting in Harrogate on page 32, and Sayan Datta, Leeds and Helen Devine, London, of the ABNT preview the meeting's trainee sessions. We welcome Sian Alexander to the editorial board. We have our usual reviews, and hope you enjoy this issue of ACNR.

*Mike Zandi, Editor.*
*Email. Rachael@acnr.co.uk*

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## Introduction to the ACNR Stroke Series

In our stroke series, we are pleased to have this article by Sunaina Yadav and Pankaj Sharma, who provide a concise and clear overview of recent advances in the genetics of ischaemic stroke. The rare monogenic diseases (e,g CADASIL, CARASIL) are discussed, as well as candidate gene and genome-wide association studies. The authors note that recent large collaborations have clearly shown the value of large sample sizes,and the importance of considering stroke mechanism in genetic studies. Indeed, the most compelling genetic associations have been for specific subtypes, for example cardioembolic or large-artery thromboembolic stroke.This article conveys the promise and excitement of this rapidly developing field, with the hope that genetics will identify new biological pathways and ultimately treatment approaches for ischaemic stroke."

*David Werring, Reader in Clinical Neurology,*
*UCL Institute of Neurology,*
*National Hospital for Neurology and Neurosurgery,*
*Queen Square, WC1N 3BG.*

# The Genetics of Ischaemic Stroke

***Sunaina Yadav, PhD***
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Nearly 15 million individuals suffer from stroke each year of which 5.5 million (10% of all global deaths) die. Stroke also consumes 2-4% of global health care costs and about 4% of direct health care costs in industrialised countries.[1] Besides the economic effects of stroke there are several social implications of the disease. Stroke leaves over 60% of the survivors with moderate to severe disability, limiting their ability to gain employment and resulting in a decline in their social functioning.[2] Stroke survivors are also known to suffer from psychological disorders such as post stroke depression[3] which results in greater mortality rates than non-depressive survivors.[4] Socio-economic status of stroke patients also affects their propensity to risk factors and mortality due to an individual's ability to access healthcare, take medication and maintain a healthy lifestyle.

### Heritability of Stroke

Up to 90% of the population attributable risk for stroke rests with ten conventional stroke risk factors including hypertension, atrial fibrillation, cigarette smoking, diabetes mellitus and obesity.[5] Management of these risk factors offers the exciting possibility of near complete elimination of stroke. However, stroke risk extends well beyond the boundaries of these risk factors and the disparity in stroke prevalence within a population that is uniformly exposed to environmental risk factors suggests that some other unknown mechanisms are at play. Some of this phenotypic variability has been attributed to genetic differences, with familial patterns of inheritance lending support.

Most family and twin studies suggest the genetic liability is greater in individuals aged younger than 70 years[6,7] and varies with stroke subtype.[8] Case-control studies suggest a 76% increase in the risk of ischaemic stroke in the presence of a family history of stroke,[6] although not all reports have demonstrated a positive relationship with family history[9] possibly due to confounding factors such as blood pressure.[10]

The genetic basis of stroke may, for practical purposes, broadly be divided between single gene (monogenic) and polygenic (complex/multifactorial, i.e. genes interacting with environmental determinants). The difference is clinically important as the monogenic diseases have a higher penetrance and larger effect size, while polygenic presence may have lower penetrance but likely be more prevalent in the population and may be countered by managing modifiable environmental determinants (e.g. hypertension).

### Monogenic stroke studies

Monogenic stroke provides the most convincing evidence for the genetic aetiology of human stroke and genes have been identified using solely the distribution of genotypes and phenotypes within narrowly delimited families to determine the location of disease loci.[11] While stroke remains principally a common sporadic disorder, our understanding of monogenic forms of stroke has improved greatly in recent times.[12,13] However, these rare forms of stroke account for only a small percentage of stroke incidence and while not useful for determining the incidence of sporadic or polygenic forms of ischaemic stroke that affect the general population they may be extremely useful in improving our understanding of the underlying mechanisms involved in the more common disorder.

### CADASIL

Described by Joutel et al in 1996,[14] CADASIL is a Mendelian form of hereditary small-vessel disease and vascular dementia. Over 100 pathogenic mutations in the *NOTCH3* gene, an evolutionarily highly conserved transmembrane receptor protein regulating cell fate,[15] are known to almost always lead to an odd number of cysteine residues in one of the 33 EGF like repeats in the extracellular domain of the Notch3 protein. These mainly missense mutations are thought to result in conformational changes of the Notch3 protein. Mutations have predominately been identified in individuals of European descent, although cases have been

found in other populations such as South Asia.[16] A recent sequencing study has shown the association between common variants in the *NOTCH3* gene and increase in the risk of age-related white matter hyperintensities in hypertensives, suggesting that *NOTCH3* may play an important role in sporadic stroke as well.[17,18]

The prevalence of CADASIL is likely underestimated, as clinical suspicion along with laboratory diagnosis is required. There are few prevalence studies, with one registry in Scotland, UK estimating prevalence rate of confirmed CADASIL cases of 1.98/100,000.[19] Genotype-phenotype correlations have been difficult to determine precisely, mainly because of the heterogeneous nature of the mutations, although some mutations are associated with a worse prognosis.[20,21] Adding to this problem, CADASIL-like symptoms have also been observed in patients without *NOTCH3* mutations[22]. Phenotypic differences such as higher volume of white matter hyperintensities have also been observed in patients with mutations in the *NOTCH3* Delta/Serrate/LAG-2 (DSL) ligand-binding domain as compared to patients with mutations outside of the DSL-binding domain.[23]

Studies investigating CADASIL in monozygotic twins with the *NOTCH3* Cys251Tyr mutation demonstrated significant phenotypic differences in the severity of disease. The study hinted at interplay of genes and environment, with the physically inactive-smoking twin suffering a stroke 14 years earlier than the twin who led an active and healthy lifestyle.[24]

There is no cure for CADASIL with treatment mainly directed at aggressive vascular risk management.

### CARASIL

CARASIL or Maeda syndrome[25] is caused by mutations in *HTRA1* gene localised on Chr10q encoding *HTRA1* that represses signalling mediated by Transforming Growth Factor β (TGF-β) family.[26] Resultantly, CARASIL patients have unproteolised cellular proteins, which affect the signal transduction process. Brain MRI shows diffuse white matter changes and multiple lacunar infarctions in the basal ganglia and thalamus.[27] Histopathologically, arteriosclerosis is seen in the penetrating arteries in the absence of granular osmiophilic or amyloid material.[28] Compared to CADASIL, CARASIL patients are also less likely to have migraines and exhibit psychiatric disorders, such as euphoria and emotional lability.[13]

Prevalence rates for CARASIL are lower than CADASIL, although it is probably more frequent than the few dozen currently reported cases, which to-date have only been described from Japan and China.[27]

### Fabry's Disease

Fabry's disease is a congenital metabolic disorder caused by deficient activity of α-galactosidase A, resulting in a progressive accumulation of globotriaosylceramide and related glycosphingolipids within vascular endothelial cells, myocardial cells and neurons.[29] Prevalence rate of Fabry's is unclear with studies reporting different results. A German study by Rolf et al reported the prevalence of Fabry's in young male stroke patients as 4.9%[30] and suggested that Fabry's could be a common cause of cryptogenic ischaemic stroke. Another multi-racial study refutes this finding reporting Fabry's disease in 0.18% of all strokes and 0.65% of cryptogenic strokes.[31] Although an X-linked lysosomal storage disorder, female carriers can develop symptoms[32] that appear comparatively later in life as compared to males, at a median age of 45.7 years.[33]

Treatment for Fabry's includes bi-weekly recombinant α-gal enzyme replacement therapy at a dose of 1mg/kg body weight, however, continued management of conventional stroke risk factors is important as well.[34]

### MELAS

MELAS is one of the most clinically prevalent and commonly encountered genetic disorders, 80% of which is accounted for by maternally transmitted mitochondrial tRNA (Leu) A3243G mutations.[35] Another 10% of patients carry the T3271C mutation. The prevalence of MELAS varies from 7.9/100,000 in England to 236/100,000 in Australia[36] with an age of onset ranging from 2 to 20 years.

Treatments for MELAS are varied and include the use of vitamin supplements (B complex, E and C) and enzyme co-factors (Q10, idebenone) that enhance mitochondrial metabolism and respiratory chain activity.[34]

### Other Monogenic Disorders

A number of other monogenic disorders have also been associated with stroke; Marfan syndrome,[12] Sickle cell disease,[13] homocystinuria[37] and systemic lupus erythematosus.[38] For a more detailed review of these disorders we direct the reader to the book 'Stroke Genetics' published in 2012 by Springer (Editors Pankaj Sharma & James Meschia).

### Strategies to Study Genetics of Stroke

With the emergence of large stroke consortia and developments in genotyping technology, statistical methods and computational power, researchers have finally begun to address the genetics of ischaemic stroke effectively. Advances in our knowledge of the molecular underpinnings of stroke will enable scientists and clinicians to better understand the mechanistic workings of stroke and design effective treatments for it.

Evidence for stroke genetics can come from two different platforms; study of individuals and population based studies. Study of individuals can help identify genetic variants that causally affect stroke and provides concrete evidence for the genetic risk of stroke. Individual studies usually identify rare genetic variants with large effect sizes and high penetrance. Although such studies are of immense value, they rarely contribute to the prevention of stroke at a population level since it involves a large number of individuals at a small risk of stroke which gives rise to more cases of disease than a small number who are at high risk.[39] Individual based studies have led to the identification of several monogenic forms of stroke such as CADASIL[14] and enabled clinicians to use this information in their everyday clinical practice.

Population based genetic association studies have found great popularity with genetic epidemiologists since the study samples are more representative of the general population and easier to recruit as compared to stroke families. Results from a large population study are useful in calculating population attributable risk (PAR) of a genetic variant, which can be extrapolated to the general population. Population studies also have greater power in detecting common genetic variants that affect >5% of the population.

### Candidate gene based studies

The study of candidate genes are often based on a priori hypothesis, primarily driven by the choice of a candidate gene which is based on the investigator's research interest in a particular biological pathway such as coagulation, lipid metabolism, inflammation and blood pressure regulation,[40-43] or candidate genes derived from related vascular conditions such as MI[44] or CAD.[45] This is not surprising as the pathophysiology of stroke and coronary disease are similar.[46] However, replication of such candidate genes in other phenotypes has not always been successful,[47] with some candidates appearing to be organ-specific rather than pathophysiology-specific.[48,49] Candidate genes found to be associated with stroke in one ethnic population are also routinely replicated in other ethnicities.[50,51] Genes involved in lipid metabolism and enzymatic activities are the most widely studied candidates for association with stroke.[52]

Recently, findings from candidate gene association studies in stroke and other vascular phenotypes such as CAD and AF were replicated using statistically robust GWAS models. Using >3500 stroke cases and 5700 controls from the WTCCC-2 (Wellcome Trust Case Control Consortium) ischaemic stroke GWAS[53] association for 50 previously reported candidate genes were tested.[54] Of the 32 stroke associated genes tested, 4 genes *ALOX5AP* (CE), *APOA (LPA)* (SVD), *Fibrinogen* (all ischaemic stroke), and *Paroxonase-1* (SVD) survived Bonferroni correction but failed when the more stringent Nyholt correction was applied. The study also tested 18 genes associated with cardiovascular phenotypes and validated the association for 3 genes at the modified Nyholt threshold: *PHACTR1* in LVD ($P=2.63\times10^{-6}$), *PITX2* in CE stroke ($P=4.78\times10^{-8}$), and *ZFHX3* in CE stroke ($P=5.50\times10^{-7}$). Given the failure to replicate most stroke associated genes, the study concluded that the risk association is likely to be sub-type specific and success in

**Table 1: Risk of ischaemic stroke in different vascular beds. (Adapted from Bentley et al., 2010)**

| Gene | Polymorphism | MI/IHD | IS | Effect |
|---|---|---|---|---|
| Factor V Leiden | Arg506Gln | 1.17 (1.08-1.28) | 1.25 (1.08-1.45) | MI=IS |
| ACE | I/D | 1.21 (1.11-1.32) | 1.15 (1.06-1.25) | MI=IS |
| MTHFR | C677T | 1.16 (1.05-1.28) | 1.27 (1.08-1.48) | MI=IS |
| Prothrombin | G20210A | 1.25 (1.05-1.50) | 1.62 (1.29-2.04) | IS>MI |
| Glycoprotein IIIa | Leu33Pro | 1.02 (0.96-1.07) | 1.20 (1.08-1.34) | IS only |
| PAI-1 | [-675]4G | 1.06 (1.02-1.10) | 0.90 (0.82-0.99) | >MI<IS* |
| Angiotensinogen | M235T | 1.11 (1.03-1.19) | 0.96 (0.87-1.02) | >MI<IS* |
| Apolipoprotein E | E4/E3 | 1.18 (1.05-1.33) | 1.24 (0.92-1.67) | MI=IS |
| Factor XIII | Leu/Val | 0.84 (0.76-0.94) | 0.95 (0.68-1.32) | <MI<IS |
| ACE receptor | A1166C | 1.13 (1.04-1.23) | 1.23 (1.09-1.39) | MI=IS |
| eNOS | Glu298Asp | 1.31 (1.13-1.51) | 1.08 (0.87-1.35) | MI>IS |

* Risk of Myocardial infarction (MI) and/or ischaemic heart disease (IHD) but protective in Ischaemic stroke.

identifying risk variants would continue to evade researchers unless the study populations are larger and extensively sub-typed.

Candidate gene studies have also been applied to test the progression of stroke through its intermediate phenotypes. Adib-Samii et al examined the 17q25 locus that was previously found to be associated with white matter hyperintensities in stroke-free individuals and replicated the association with white matter hyperintensity volume in ischaemic stroke patients to determine whether the 17q25 locus promotes small vessel arteriopathy. The study furnished evidence in support of an association between 17q25 and white matter hyperintensities.[55]

Similarly, search for blood pressure genes by the International Consortium for blood pressure genome-wide association studies (ICGP 2011) in 200,000 individuals of European descent identified 16 novel loci whose cumulative genetic risk score (in addition to 13 other loci) was associated with stroke.[56] Hypertension being the biggest risk factor for stroke, rendered this an anticipated finding. Besides the 'routine' phenotypes of blood pressure such as systolic BP, diastolic BP, mean arterial pressure and pulse pressure, the genetics of long-term variability in blood pressure or episodic hypertension have also been investigated. In a recent study, the ASCOT IR-UK cohort identified an association between NLGN1 gene and BP variability but could not replicate the association in a large ischaemic stroke population comprising 8624 cases and 12722 controls.[57]

Unique step-back approaches have also been implemented to test association of candidate genes with stroke. A study by Krug et al performed gene expression profiling in peripheral blood mononuclear cells of 20 stroke cases and 20 controls and examined the differentially expressed genes between the two groups. Sixteen differentially expressed genes were then mapped to GWAS-derived regions associated with various vascular disorders. Using this approach the group was able to identify a risk association between stroke and the *TTC7B* gene locus.[58]

Over all, results from candidate gene studies suggest that common stroke has a genetic component with several genes exerting individual modest effects but no single gene having a major effect. Meta-analyses of these studies has allowed disease associated genes to be reliably identified and assigned odds ratios with much greater robustness (OR 1.1-1.8) depending on the gene of interest.[48,59] Candidate gene studies have also demonstrated that genetic risk associations

**Table 2: Genome wide association studies on ischaemic stroke**

| Gene | SNP | Chr | Phenotype | Ethnicity | RA | RAF |
|---|---|---|---|---|---|---|
| ALDH2 | rs10744777 | 12q24.12 | IS | European | -- | -- |
| HDAC9 | rs2107595 | 7p21.1 | LVD | European | A | 0.16 |
| PITX2 | rs6843082 | 4q25 | CE | European | G | 0.21 |
| CDKN2A/B | rs2383207 | 9p21.3 | LVD | European | G | 0.52 |
| ZFHX3 | rs879324 | 16q22.3 | CE | European | A | 0.19 |
| CDC5L | rs556621 | 6p21.1 | LVD | European | A | -- |
| FMNL2 | rs2304556 | 2q23.3 | YS | European/African | G | -- |
| ARL6IP6 | rs1986743 | 2q23.3 | YS | European/African | A | -- |
| ROBO1 | rs1383407 | 3p12.2 | IS | European | C | 0.44 |
| NINJ2 | rs11833579 | 12p13.33 | IS | European | A | 0.23 |
| CELSR1 | rs6007897 | 22 | IS | Japanese | G | -- |
| AGTRL1 | rs9943582 | 11q12 | IS | Japanese | G | -- |
| PRKCH | rs1452 | 14q22–q23 | SVD | Japanese | A | 0.23 |
| ALOX5AP | HapA (SG13S25, SG13S114, SG13S89 and SG13S32) | 13q12-13 | IS | European | -- | 0.09 ↟ |
| PDE4D | | 5q12 | CE & cryptogenic | European | -- | 0.16 |

*All p values are the lowest ever reported for a SNP by the main study under the 'Study' heading.

for ischaemic stroke are broadly similar across different ethnicities, with some notable exceptions.[60,61] Such studies have also implicated disparity in the genetic burden of stroke for different stroke subtypes[62,63] long before this was discovered in large-scale GWA studies.[64]

Candidate gene studies demonstrate that while the effect sizes per gene were small, the sum of the PARs across all associations is ~30% and given the relative frequency of stroke, translates to a large clinically observed effect, although publication bias may be a reason for this probably inflated size estimate. Using a Mendelian randomisation methodology, some candidate genes (*MTHFR, Factor V Leiden, ACE, Prothrombin* and *PAI-1*) have gone on to be not just associated with stroke but causally linked.[48] Some of these genes are associated with an ischaemic process per se (e.g. with stroke and ischaemic heart disease) while others are stroke specific (Table 1).[48]

**Genome wide association studies**

The natural extension of studying single gene regions in the human chromosome to studying all regions (of millions of genetic variants in a single experiment), and thereby avoiding investigator bias, has led to an explosion in genome wide association studies. As these studies are conducted without an a priori hypothesis, these have the added advantage of potentially identifying new and unpredictable genes, which could eventually lead to the development of novel therapeutic targets. The emergence of genome wide approaches have also presented investigators with an alternative and more powerful method to test the productivity of the candidate gene based approach.[54]

Powerful GWA studies have been made possible by the advent of the human genome project and the HapMap consortium. With completion of the Human Genome Project in 2003, scientists identified regions of variation between individuals, the most common form of which is the single nucleotide polymorphism or SNP. The human genome is believed to consist of over 10 million SNPs and, with the efforts of the International HapMap project, 3 million SNPs have been characterised.[65] Information provided by HapMap has enabled the development of commercially available genotyping microarrays, which heralded the era of the GWA study. In recent times the 1000 Genomes project (http://www.1000genomes.org) has provided 4X deep sequencing data and added immensely to the knowledge base. As technology used to unravel the genetic basis of disease has advanced, our ability to rapidly and inexpensively search for susceptibility loci has dramatically improved. Individual candidate gene studies have predominantly been replaced by whole-genome screening, which has been successfully conducted in a variety of disorders including bipolar disorder, CAD, Crohn's disease, hypertension, rheumatoid arthritis and diabetes (NHGRI catalogue, http://www.genome.gov/gwastudies/).

One of the first major GWAS in stroke was published in 2003, which identified phosphodiesterase 4D (PDE4D) to be significantly associated with risk of ischaemic stroke in an Icelandic population.[66] However several attempts to replicate these findings failed, while others reported conflicting results. These discrepancies were attributed to possible problems in study design, i.e. not accounting for stroke sub-type heterogeneity.

The WTCCC-2 and the ISGC (International Stroke Genetics Consortium) performed a GWAS involving 3,548 cases of ischaemic stroke with replication of potential signals in 5,859 additional cases.[53] The study demonstrated, as others had done previously,[67,68] associations for CE stroke near *PITX2* and *ZFHX3*, which are known risk loci for AF.[69] The study also confirmed the association for LVD and 9p21 locus. A novel finding was an association for large vessel stroke within *HDAC9* on chromosome 7p21.1 (OR 1.42). In a recent GWAS, the evidence for a stroke sub-type specific genetic influence became more compelling with the association of the 6p21.1 locus with large artery stroke subtype.[64] The METASTROKE meta-analysis, (~12,000 cases and ~60,000 controls) further validated previous findings of genes *PITX2*, *ZFHX3*, and *HDAC9* suggesting that these were true associations.[70] All loci exhibited heterogeneous effect across subtypes, supporting distinct genetic architectures for each subtype. The largest and most recent GWAS consisting of 17,900 ischaemic stroke cases failed to replicate the METASTROKE findings but identified a novel locus at 12q24.12.[71]

Several other GWAS have been conducted in stroke mostly in those of European descent, with very little comparative data available in other ethnic populations. A few studies have been conducted in populations of Asian ancestry[72-74] with broadly similar effect sizes (<1.85). Many studies, however, have failed to replicate their findings.[75-77]

Noting that some ischaemic stroke has a maternal heritability, a GWAS of common mitochondrial sequence variants failed to find a genome significance threshold, although this study was underpowered for GWAS.[78] GWA studies on stroke twins found no significant hits but were able to demonstrate significant correlation of age at stroke within pairs of affected siblings (r=0.83, 95% CI 0.78–

| | OR (95% CI) | p | Study | Other studies |
|---|---|---|---|---|
| | 1.10 (1.07-1.13) | 7.12 ×10-11 | (Kilarski et al 2014) | -- |
| | 1.39 (1.27-1.53) | 2.03 ×10-16 | (Traylor et al., 2012) | (International Stroke Genetics et al., 2012) |
| | 1.36 (1.27-1.47) | 2.8×10-16 | (Traylor et al., 2012) | (Gudbjartsson et al., 2007, Gretarsdottir et al., 2008, International Stroke Genetics et al., 2012) |
| | 1.15 (1.08-1.23) | 3.32×10-5 | (Traylor et al., 2012) | (Matarin et al., 2008, International Stroke Genetics et al., 2012) |
| | 1.25 (1.15-1.35) | 2.28×10-8 | (Traylor et al., 2012) | (Gudbjartsson et al., 2009) |
| | 1.21 (1.13-1.30) | 4.70×10-8 | (Holliday et al., 2012a) | -- |
| | 0.69 (0.60, 0.79) | 1.20×10-7 | (Cheng et al., 2011) | -- |
| | 0.69 (0.60, 0.79) | 2.70×10-7 | (Cheng et al., 2011) | -- |
| | 0.96 | 7.63×10-5 | (Meschia et al., 2011) | -- |
| | 1.41 (1.27-1.56) | 2.3×10-10 | (Ikram et al., 2009) | (Traylor et al., 2012) |
| | 1.85 (1.29-2.61) | 6.00×10-4 | (Yamada et al., 2009) | -- |
| | 1.30 (1.14-1.47) | 6.66×10-5 | (Hata et al., 2007) | -- |
| | 1.40 (1.23-1.59) | 5.10×10-7 | (Kubo et al., 2007) | -- |
| | 1.67 | 9.50×10-5 | (Helgadottir et al., 2004) | -- |
| | -- | 1.50×10-6 | (Gretarsdottir et al., 2003) | -- |

**'Other Studies' are studies that have also reported a GWAS significant association for a SNP. † RAF reported in controls only

0.86, p=2.2x10-16) and high concordance of stroke subtypes among affected pairs (33.8%, kappa=0.13, p=5.06x10-4) which did not differ by age at stroke in the proband.[79] Some investigators have undertaken GWAS on surrogate markers such as white matter hypertensities intermediate phenotypes[80] or intermediate phenotypes such as intima-media thickness.[81]

Reports of a new wave of GWA studies are underway, including the WTCCC-2 and NINDS Stroke Genetics Network,[82] which will utilise the CCS classification system.[83] The studies will focus entirely on sub-typing a large number of ischaemic stroke cases. A total of 24 genetic research centres across Europe and America will participate in this global consortium amassing over 14,549 stroke cases.[82] Large-scale prospective case-control studies examining ethnic/racial variances in ICH are also in the making[84] and are likely to extend to ischaemic stroke in the near future.

GWA studies are not a panacea for identifying genetic loci, suffering several important limitations. Errors in genotyping, quality control, and choice of analytical methods can lead to false positive results. The European population is genetically stratified[85] and a mixture of populations with different ancestry can also lead to inflated statistics. Results from large GWA studies have implied that dissecting out the susceptibility genes for stroke needs to consider its subtypes as different entities. This should not be surprising, as stroke is a clinical syndrome encompassing any sudden focal neurological deficit from a vascular aetiology. Notwithstanding the arguments about sub-typing, a recent GWAS provided evidence for a genetic influence on all-cause ischaemic stroke.[64] GWA studies also provide a limited understanding of the gene-environment interaction, which may play a major role in the differential gene expression. Another major limitation of the GWA study model is its inability to identify common genetic variants (>5%) with large effect sizes that exert an effect measureable at the population level. Most published studies have identified common variants with small to modest effect sizes for dichotomous traits (OR <1.5) and variance of <1% for quantitative traits.[86]

## Genotyping and gene expression platforms

DNA microarrays allow researchers the ability to undertake high-throughput gene expression. Rapid growth in microarray technology has been spearheaded by companies such as Illumina (San Diego, USA) and Affymetrix (Santa Clara, USA), which differ considerably in SNP selection strategy and hybridisation chemistry.[87]

These technologies are reliant on the availability of large, well-characterised bio banks. A number of stroke specific DNA repositories exist and our own biobank, Bio Repository of DNA in Stroke (BRAINS) is composed of samples from those of European descent in the UK, British Asians, Indians living in India and Middle Eastern's in Qatar (www.BrainsGenetics.com). This international repository should allow a unique comparison between disparate ancestral stroke populations.[88,89]

## Next generation sequencing

Just as candidate genes were regarded as a stepping-stone to GWAS, the latter may be regarded as a stepping-stone to Next Generation Sequencing (NGS) which will allow deep sequencing of the human genome and detection of 'rare variant, common disease'. As the cost of whole genome sequencing has plummeted in the last decade (from $100million per genome in 2001 to $8thousand per genome in 2014) (www.genome.gov), NGS is likely to greatly advance our understanding in stroke – where bio-repositories will be well placed to take advantage.

Although the HapMap database has some rare variants, it is mostly the common SNPs that are genotyped. The general perception is that the 'missing heritability 'of stroke lies with rare genetic variants, which are too infrequent to be picked up by commercially available genotyping platforms. The availability of the entire human genome via HapMap aided by advances in statistical computation makes it a promising strategy for studying genetics of stroke. The 1000 Genomes project with whole genomes of 1000 healthy individuals will further provide dense coverage of both common and rare variants and add important information to the current knowledge base.

Although large-scale NGS approaches are already in the pipeline for various disease traits, currently there have been no published NGS studies on common stroke.

## Conclusion

The genetic aetiology of stroke is currently the subject of intense international collaborative efforts. It is unlikely that a single gene will be responsible for sporadic age-related stroke; rather multiple genes acting with environmental determinants will decide eventual susceptibility. This is an exciting time in stroke genetics with promises of understanding its molecular mechanisms likely to be honoured, potential novel therapeutic targets identified and pharmacological interventions being directed by genotyping in a more personalised medicine approach.

REFERENCES


1. Donnan GA, Fisher M, Macleod M, et al. *Stroke.* Lancet 2008;371(9624):1612-23 doi: 10.1016/S0140-6736(08)60694-7[published Online First: Epub Date]|.
2. Sreedharan SE, Unnikrishnan JP, Amal MG, et al. *Employment status, social function decline and caregiver burden among stroke survivors. A South Indian study.* Journal of the neurological sciences 2013;332(1-2):97-101 doi: 10.1016/j.jns.2013.06.026[published Online First: Epub Date]|.
3. Chatterjee K, Fall S, Barer D. *Mood after stroke: a case control study of biochemical, neuro-imaging and socio-economic risk factors for major depression in stroke survivors.* BMC neurology 2010;10:125 doi: 10.1186/1471-2377-10-125[published Online First: Epub Date]|.
4. Paul N, Das S, Hazra A, et al. *Depression Among Stroke Survivors: A Community-based, Prospective Study from Kolkata, India.* The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2013;21(9):821-31 doi: 10.1016/j.jagp.2013.03.013[published Online First: Epub Date]|.
5. O'Donnell MJ, Xavier D, Liu L, et al. *Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study.* Lancet 2010;376(9735):112-23 doi: 10.1016/S0140-6736(10)60834-3[published Online First: Epub Date]|.
6. Flossmann E, Schulz UG, Rothwell PM. *Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke.* Stroke; a journal of cerebral circulation 2004;35(1):212-27 doi: 10.1161/01.STR.0000107187.84390.AA[published Online First: Epub Date]|.
7. Jood K, Ladenvall P, Tjarnlund-Wolf A, et al. *Fibrinolytic gene polymorphism and ischemic stroke.* Stroke; a journal of cerebral circulation 2005;36(10):2077-81 doi: 10.1161/01.STR.0000183617.54752.69[published Online First: Epub Date]|.
8. Schulz UG, Flossmann E, Rothwell PM. *Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies.* Stroke; a journal of cerebral circulation 2004;35(4):819-24 doi: 10.1161/01.STR.0000121646.23955.0f[published Online First: Epub Date]|.
9. Flossmann E, Rothwell PM. *Family history of stroke does not predict risk of stroke after transient ischemic attack.* Stroke; a journal of cerebral circulation 2006;37(2):544-6 doi: 10.1161/01.STR.0000198879.11072.f2[published Online First: Epub Date]|.
10. Flossmann E, Rothwell PM. *Family history of stroke in patients with transient ischemic attack in relation to hypertension and other intermediate phenotypes.* Stroke; a journal of cerebral circulation 2005;36(4):830-5 doi: 10.1161/01.STR.0000158920.67013.53[published Online First: Epub Date]|.
11. Devlin B, Roeder K. *Genomic control for association studies.* Biometrics 1999;55(4):997-991004.
12. Della-Morte D, Guadagni F, Palmirotta R, et al. *Genetics of ischemic stroke, stroke-related risk factors, stroke precursors and treatments.* Pharmacogenomics 2012;13(5):595-613 doi: 10.2217/pgs.12.14[published Online First: Epub Date]|.
13. Muqtadar H, Testai FD. *Single gene disorders associated with stroke: a review and update on treatment options.* Current treatment options in cardiovascular medicine 2012;14(3):288-97 doi: 10.1007/s11936-012-0179-4[published Online First: Epub Date]|.
14. Joutel A, Corpechot C, Ducros A, et al. *Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia.* Nature 1996;383(6602):707-10.
15. Artavanis-Tsakonas S, Rand MD, Lake RJ. *Notch signaling: cell fate control and signal integration in development.* Science 1999;284(5415):770-76.
16. Yadav S, Bentley P, Srivastava P, et al. *The first Indian-origin family with genetically proven cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).* Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2013;22(1):28-31 doi: 10.1016/j.jstrokecerebrovasdis.2011.05.023[-published Online First: Epub Date]|.
17. Ross OA, Soto-Ortolaza AI, Heckman MG, et al. *Variants and Risk of Ischemic Stroke.* PloS one 2013;8(9):e75035 doi: 10.1371/journal.pone.0075035[published Online First: Epub Date]|.

18. Schmidt H, Zeginigg M, Wiltgen M, et al. *Genetic variants of the NOTCH3 gene in the elderly and magnetic resonance imaging correlates of age-related cerebral small vessel disease.* Brain : a journal of neurology 2011;134(Pt 11):3384-97 doi: 10.1093/brain/awr252[published Online First: Epub Date]|.
19. Razvi SS, Davidson R, Bone I, et al. *The prevalence of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) in the west of Scotland.* Journal of neurology, neurosurgery, and psychiatry 2005;76(5):739-41 doi: 10.1136/jnnp.2004.051847[published Online First: Epub Date]|.
20. Monet-Lepretre M, Bardot B, Lemaire B, et al. *Distinct phenotypic and functional features of CADASIL mutations in the Notch3 ligand binding domain.* Brain : a journal of neurology 2009;132(Pt 6):1601-12 doi: 10.1093/brain/awp049[published Online First: Epub Date]|.
21. Opherk C, Peters N, Herzog J, et al. *Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients.* Brain : a journal of neurology 2004;127(Pt 11):2533-9 doi: 10.1093/brain/awh282[published Online First: Epub Date]|.
22. Pantoni L, Pescini F, Nannucci S, et al. *Comparison of clinical, familial, and MRI features of CADASIL and NOTCH3-negative patients.* Neurology 2010;74(1):57-63.
23. Meschia JF. *New information on the genetics of stroke.* Current neurology and neuroscience reports 2011;11(1):35-41 doi: 10.1007/s11910-010-0155-x[published Online First: Epub Date]|.
24. Mykkanen K, Junna M, Amberla K, et al. *Different clinical phenotypes in monozygotic CADASIL twins with a novel NOTCH3 mutation.* Stroke; a journal of cerebral circulation 2009;40(6):2215-8 doi: 10.1161/STROKEAHA.108.528661[published Online First: Epub Date]|.
25. Fukutake T, Hirayama K. *Familial young-adult-onset arteriosclerotic leukoencephalopathy with alopecia and lumbago without arterial hypertension.* Eur Neurol 1995;35(2):69-79.
26. Hara K, Shiga A, Fukutake T, et al. *Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease.* The New England journal of medicine 2009;360(17):1729-39 doi: 10.1056/NEJMoa0801560[published Online First: Epub Date]|.
27. Fukutake T. *Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): from discovery to gene identification.* Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2011;20(2):85-93 doi: 10.1016/j.jstrokecerebrovasdis.2010.11.008[published Online First: Epub Date]|.
28. Arima K, Yanagawa S, Ito N, et al. *Cerebral arterial pathology of CADASIL and CARASIL (Maeda syndrome).* Neuropathology : official journal of the Japanese Society of Neuropathology 2003;23(4):327-34.
29. Toyooka K. *Fabry disease.* Current opinion in neurology 2011;24(5):463-8 doi: 10.1097/WCO.0b013e32834a9433[published Online First: Epub Date]|.
30. Rolfs A, Bottcher T, Zschiesche M, et al. *Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study.* Lancet 2005;366(9499):1794-6 doi: 10.1016/S0140-6736(05)67635-0[published Online First: Epub Date]|.
31. Wozniak MA, Kittner SJ, Tuhrim S, et al. *Frequency of unrecognized Fabry disease among young European-American and African-American men with first ischemic stroke.* Stroke; a journal of cerebral circulation 2010;41(1):78-81 doi: 10.1161/STROKEAHA.109.558320[published Online First: Epub Date]|.
32. Wilcox WR, Oliveira JP, Hopkin RJ, et al. *Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry.* Molecular genetics and metabolism 2008;93(2):112-28 doi: 10.1016/j.ymgme.2007.09.013[published Online First: Epub Date]|.
33. Sims K, Politei J, Banikazemi M, et al. *Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry.* Stroke; a journal of cerebral circulation 2009;40(3):788-94 doi: 10.1161/STROKEAHA.108.526293[published Online First: Epub Date]|.
34. Sharma P, Yadav S, Meschia JF. *Genetics of ischaemic stroke.* Journal of neurology, neurosurgery, and psychiatry 2013 doi: 10.1136/jnnp-2012-304834[published Online First: Epub Date]|.
35. Goto Y, Horai S, Matsuoka T, et al. *Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): a correlative study of the clinical features and mitochondrial DNA mutation.* Neurology 1992;42(3 Pt 1):545-50.
36. Manwaring N, Jones MM, Wang JJ, et al. *Population prevalence of the MELAS A3243G mutation.* Mitochondrion 2007;7(3):230-3 doi: 10.1016/j.mito.2006.12.004[published Online First: Epub Date]|.
37. Kelly PJ, Furie KL, Kistler JP, et al. *Stroke in young patients with hyperhomocysteinemia due to cystathionine beta-synthase deficiency.* Neurology 2003;60(2):275-79.
38. Troedson C, Wong M, Dalby-Payne J, et al. *Systemic lupus erythematosus due to C1q deficiency with progressive encephalopathy, intracranial calcification and acquired moyamoya cerebral vasculopathy.* Lupus 2013;22(6):639-43.
39. Rose FC. *Problems in the management of stroke.* Ann Acad Med Singapore 1985;14(1):12-15.
40. Matarin M, Brown WM, Hardy JA, et al. *Association of integrin alpha2 gene variants with ischemic stroke.* Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2008;28(1):81-9 doi: 10.1038/sj.jcbfm.9600508[published Online First: Epub Date]|.
41. Williams FM, Carter AM, Hysi PG, et al. *Ischemic stroke is associated with the ABO locus: the EuroCLOT study.* Annals of neurology 2013;73(1):16-31 doi: 10.1002/ana.23838[published Online First: Epub Date]|.
42. Wang X, Cheng S, Brophy VH, et al. *A meta-analysis of candidate gene polymorphisms and ischemic stroke in 6 study populations: association of lymphotoxin-alpha in nonhypertensive patients.* Stroke; a journal of cerebral circulation 2009;40(3):683-95 doi: 10.1161/STROKEAHA.108.524587[published Online First: Epub Date]|.
43. Olsson S, Holmegaard L, Jood K, et al. *Genetic variation within the interleukin-1 gene cluster and ischemic stroke.* Stroke; a journal of cerebral circulation 2012;43(9):2278-82 doi: 10.1161/STROKEAHA.111.647446[published Online First: Epub Date]|.
44. Gschwendtner A, Bevan S, Cole JW, et al. *Sequence variants on chromosome 9p21.3 confer risk for atherosclerotic stroke.* Annals of neurology 2009;65(5):531-9 doi: 10.1002/ana.21590[published Online First: Epub Date]|.
45. Arregui M, Fisher E, Knuppel S, et al. *Significant associations of the rs2943634 (2q36.3) genetic polymorphism with adiponectin, high density lipoprotein cholesterol and ischemic stroke.* Gene 2012;494(2):190-5 doi: 10.1016/j.gene.2011.12.009[published Online First: Epub Date]|.
46. Jashari F, Ibrahimi P, Nicoll R, et al. *Coronary and carotid atherosclerosis: Similarities and differences.* Atherosclerosis 2012 doi: 10.1016/j.atherosclerosis.2012.11.008[published Online First: Epub Date]|.
47. Cheng YC, Anderson CD, Bione S, et al. *Are myocardial infarction--associated single-nucleotide polymorphisms associated with ischemic stroke?* Stroke; a journal of cerebral circulation 2012;43(4):980-6 doi: 10.1161/STROKEAHA.111.632075[published Online First: Epub Date]|.
48. Bentley P, Peck G, Smeeth L, et al. *Causal relationship of susceptibility genes to ischemic stroke: comparison to ischemic heart disease and biochemical determinants.* PloS one 2010;5(2):e9136 doi: 10.1371/journal.pone.0009136[published Online First: Epub Date]|.
49. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. *Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism.* Journal of the American College of Cardiology 2012;60(8):722-9 doi: 10.1016/j.jacc.2012.01.078[published Online First: Epub Date]|.
50. Cheong MY, Bang OS, Cha MH, et al. *Association of the adiponectin gene variations with risk of ischemic stroke in a Korean population.* Yonsei medical journal 2011;52(1):20-5 doi: 10.3349/ymj.2011.52.1.20[published Online First: Epub Date]|.
51. Kostulas K, Gretarsdottir S, Kostulas V, et al. *PDE4D and ALOX5AP genetic variants and risk for Ischemic Cerebrovascular Disease in Sweden.* Journal of the neurological sciences 2007;263(1-2):113-7 doi: 10.1016/j.jns.2007.06.042[published Online First: Epub Date]|.
52. Stankovic S, Asanin M, Majkic-Singh N. *Genetics of Ischemic Stroke: Emphasis on Candidate-Gene Association Studies,* 2012.
53. International Stroke Genetics C, Wellcome Trust Case Control C, Bellenguez C, et al. *Genome-wide association study identifies a variant in HDAC9 associated with large vessel ischemic stroke.* Nature genetics 2012;44(3):328-33 doi: 10.1038/ng.1081[published Online First: Epub Date]|.
54. Bevan S, Traylor M, Adib-Samii P, et al. *Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genomewide associations.* Stroke; a journal of cerebral circulation 2012;43(12):3161-7 doi: 10.1161/STROKEAHA.112.665760[published Online First: Epub Date]|.
55. Adib-Samii P, Rost N, Traylor M, et al. *17q25 Locus is associated with white matter hyperintensity volume in ischemic stroke, but not with lacunar stroke status.* Stroke; a journal of cerebral circulation 2013;44(6):1609-15 doi: 10.1161/STROKEAHA.113.679936[published Online First: Epub Date]|.
56. International Consortium for Blood Pressure Genome-Wide Association S, Ehret GB, Munroe PB, et al. *Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk.* Nature 2011;478(7367):103-9 doi: 10.1038/nature10405[published Online First: Epub Date]|.
57. Yadav S, Cotlarciuc I, Munroe PB, et al. *Genome-wide analysis of blood pressure variability and ischemic stroke.* Stroke 2013;44(10):2703-9 doi: 10.1161/STROKEAHA.113.002186[published Online First: Epub Date]|.
58. Krug T, Gabriel JP, Taipa R, et al. *TTC7B emerges as a novel risk factor for ischemic stroke through the convergence of several genome-wide approaches.* Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2012;32(6):1061-72 doi: 10.1038/jcbfm.2012.24[published Online First: Epub Date]|.
59. Casas JP, Hingorani AD, Bautista LE, et al. *Meta-analysis of genetic studies in ischemic stroke: thirty-two genes involving approximately 18,000 cases and 58,000 controls.* Archives of neurology 2004;61(11):1652-61 doi: 10.1001/archneur.61.11.1652[published Online First: Epub Date]|.
60. Yadav S, Hasan N, Marjot T, et al. *Detailed analysis of gene polymorphisms associated with ischemic stroke in South Asians.* PloS one 2013;8(3):e57305 doi: 10.1371/journal.pone.0057305[published Online First: Epub Date]|.
61. Ariyaratnam R, Casas JP, Whittaker J, et al. *Genetics of ischaemic stroke among persons of non-European descent: a meta-analysis of eight genes involving approximately 32,500 individuals.* PLoS medicine 2007;4(4):e131 doi: 10.1371/journal.pmed.0040131[published Online First: Epub Date]|.
62. Kostulas N, Markaki I, Kostulas V, et al. *Common CCR 5 polymorphism in stroke: the CCR 5 delta32 polymorphism differentiates cardioembolism from other aetiologies of ischaemic cerebrovascular diseases.* Scandinavian journal of immunology 2009;70(5):475-80 doi: 10.1111/j.1365-3083.2009.02323.x[published Online First: Epub Date]|.
63. Anderson CD, Biffi A, Nalls MA, et al. *Common variants within oxidative phosphorylation genes influence risk of ischemic stroke and intracerebral hemorrhage.* Stroke; a journal of cerebral circulation 2013;44(3):612-9 doi: 10.1161/STROKEAHA.112.672089[published Online First: Epub Date]|.
64. Holliday EG, Maguire JM, Evans TJ, et al. *Common variants at 6p21.1 are associated with large artery atherosclerotic stroke.* Nature genetics 2012;44(10):1147-51 doi: 10.1038/ng.2397[published Online First: Epub Date]|.
65. Frazer KA, Ballinger DG, Cox DR, et al. *A second generation human haplotype map of over 3.1 million SNPs.* Nature 2007;449(7164):851-61 doi: 10.1038/nature06258[published Online First: Epub Date]|.
66. Gretarsdottir S, Thorleifsson G, Reynisdottir ST, et al. *The gene encoding phosphodiesterase 4D confers risk of ischemic stroke.* Nature genetics 2003;35(2):131-8 doi: 10.1038/ng1245[published Online First: Epub Date]|.
67. Gudbjartsson DF, Arnar DO, Helgadottir A, et al. *Variants conferring risk of atrial fibrillation on chromosome 4q25.* Nature 2007;448(7151):353-7 doi: 10.1038/nature06007[-published Online First: Epub Date]|.
68. Gudbjartsson DF, Holm H, Gretarsdottir S, et al. *A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke.* Nature genetics 2009;41(8):876-8 doi: 10.1038/ng.417[published Online First: Epub Date]|.

69. Ellinor PT, Lunetta KL, Albert CM, et al. *Meta-analysis identifies six new susceptibility loci for atrial fibrillation.* Nature genetics 2012;44(6):670-5 doi: 10.1038/ng.2261[published Online First: Epub Date]|.
70. Traylor M, Farrall M, Holliday EG, et al. *Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE Collaboration): a meta-analysis of genome-wide association studies.* Lancet neurology 2012;11(11):951-62 doi: 10.1016/S1474-4422(12)70234-X[published Online First: Epub Date]|.
71. Kilarski LL, Achterberg S, Devan WJ, et al. *Meta-analysis in more than 17,900 cases of ischemic stroke reveals a novel association at 12q24.12.* Neurology 2014;83(8):678-85 doi: 10.1212/WNL.0000000000000707[published Online First: Epub Date]|.
72. Kubo M, Hata J, Ninomiya T, et al. *A nonsynonymous SNP in PRKCH (protein kinase C eta) increases the risk of cerebral infarction.* Nature genetics 2007;39(2):212-7 doi: 10.1038/ng1945[published Online First: Epub Date]|.
73. Yamada Y, Fuku N, Tanaka M, et al. *Identification of CELSR1 as a susceptibility gene for ischemic stroke in Japanese individuals by a genome-wide association study.* Atherosclerosis 2009;207(1):144-9 doi: 10.1016/j.atherosclerosis.2009.03.038[published Online First: Epub Date]|.
74. Hata J, Matsuda K, Ninomiya T, et al. *Functional SNP in an Sp1-binding site of AGTRL1 gene is associated with susceptibility to brain infarction.* Human molecular genetics 2007;16(6):630-9 doi: 10.1093/hmg/ddm005[published Online First: Epub Date]|.
75. Debette S, Bis JC, Fornage M, et al. *Genome-wide association studies of MRI-defined brain infarcts: meta-analysis from the CHARGE Consortium.* Stroke; a journal of cerebral circulation 2010;41(2):210-7 doi: 10.1161/STROKEAHA.109.569194[published Online First: Epub Date]|.
76. International Stroke Genetics C, Wellcome Trust Case-Control C. *Failure to validate association between 12p13 variants and ischemic stroke.* The New England journal of medicine 2010;362(16):1547-50 doi: 10.1056/NEJMc0910050[published Online First: Epub Date]|.
77. Ikram MA, Seshadri S, Bis JC, et al. *Genomewide association studies of stroke.* The New England journal of medicine 2009;360(17):1718-28 doi: 10.1056/NEJMoa0900094[published Online First: Epub Date]|.
78. Anderson CD, Biffi A, Rahman R, et al. *Common mitochondrial sequence variants in ischemic stroke.* Annals of neurology 2011;69(3):471-80 doi: 10.1002/ana.22108[published Online First: Epub Date]|.
79. Meschia JF, Nalls M, Matarin M, et al. *Siblings with ischemic stroke study: results of a genome-wide scan for stroke loci.* Stroke; a journal of cerebral circulation 2011;42(10):2726-32 doi: 10.1161/STROKEAHA.111.620484[published Online First: Epub Date]|.
80. DeStefano AL, Atwood LD, Massaro JM, et al. *Genome-wide scan for white matter hyperintensity: the Framingham Heart Study.* Stroke; a journal of cerebral circulation 2006;37(1):77-81 doi: 10.1161/01.STR.0000196987.68770.b3[published Online First: Epub Date]|.
81. Bis JC, Kavousi M, Franceschini N, et al. *Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque.* Nature genetics 2011;43(10):940-7 doi: 10.1038/ng.920[-published Online First: Epub Date]|.
82. Meschia JF, Arnett DK, Ay H, et al. *Stroke Genetics Network (SiGN) Study: Design and Rationale for a Genome-Wide Association Study of Ischemic Stroke Subtypes.* Stroke; a journal of cerebral circulation 2013;44(10):2694-702 doi: 10.1161/STROKEAHA.113.001857[published Online First: Epub Date]|.
83. Ay H, Benner T, Arsava EM, et al. *A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System.* Stroke; a journal of cerebral circulation 2007;38(11):2979-84 doi: 10.1161/STROKEAHA.107.490896[published Online First: Epub Date]|.
84. Woo D, Rosand J, Kidwell C, et al. *The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) Study Protocol.* Stroke; a journal of cerebral circulation 2013;44(10):e120-e25 doi: 10.1161/STROKEAHA.113.002332[published Online First: Epub Date]|.
85. Lao O, Lu TT, Nothnagel M, et al. *Correlation between genetic and geographic structure in Europe.* Current biology : CB 2008;18(16):1241-8 doi: 10.1016/j.cub.2008.07.049[published Online First: Epub Date]|.
86. de Bakker PI, Ferreira MA, Jia X, et al. *Practical aspects of imputation-driven meta-analysis of genome-wide association studies.* Human molecular genetics 2008;17(R2):R122-8 doi: 10.1093/hmg/ddn288[published Online First: Epub Date]|.
87. Perkel J. *SNP genotyping: six technologies that keyed a revolution.* Nature Methods 2008;5(5).
88. Yadav S, Schanz R, Maheshwari A, et al. *Bio-Repository of DNA in stroke (BRAINS): a study protocol.* BMC medical genetics 2011;12:34 doi: 10.1186/1471-2350-12-34[published Online First: Epub Date]|.
89. Cotlarciuc I KM, Maheshwari A,Yadav S, Khan FY, Al-Hail H, de Silva R, Gorthi SP, Gupta S, Sharma SR, Sylaja PN, Prasad K, Sharma P on behalf of the BRAINS collaborators. *Bio-repository of DNA in stroke: a study protocol of three ancestral populations.* J R Soc Med Cardiovasc Dis 2012;1(10) doi: 10.1258/cvd.2012.012019[published Online First: Epub Date]|.

# Lysosomal Dysfunction in Neurodegenerative Diseases

**Summary**

- Lysosomes are subcellular organelles responsible for the physiologic turnover of cell constituents. Lysosomes are involved not only in degradation, but also in fundamental processes such as secretion, plasma membrane repair, signalling and energy metabolism.
- Lysosomal storage diseases (LSDs) describe a heterogeneous group of rare inherited disorders characterised by the accumulation of undigested or partially digested macromolecules in the lysosomes. This accumulation disrupts the cell's normal functioning and gives rise to the clinical manifestations of LSDs. LSDs affect different body organs or systems including the bones, eyes, heart, lungs, kidneys, skin, and frequently the central nervous system.
- Autophagy is a catabolic pathway through which cellular components (including dysfunctional organelles) are engulfed in vesicles (autophagosomes) and recycled upon fusion of autophagosomes with lysosomes. The block of autophagy (impaired fusion of autophagosomes with lysosomes) causes the accumulation of toxic material and contributes to neurodegeneration in LSDs. The impairment of autophagy initiates degenerative processes not only in LSDs but also in the most common form of age-related neurodegenerative diseases such as Parkinson's and Alzheimer's diseases.
- It has been demonstrated that α-synuclein, a presynaptic protein prone to misfolding, can aggregate and contribute to the pathogenesis of some neurodegenerative diseases through impaired autophagy capability in neuronal cells.
- Lysosomal-dependent α-synuclein accumulation found in LSDs might contribute to trigger neurodegeneration in these pathologies by causing α-synuclein chaperoning deficit and presynaptic failure.

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## Introduction

Lysosomal storage diseases (LSDs) are a family of disorders resulting from inherited gene mutations that perturb lysosomal homeostasis, thus ultimately leading to the accumulation of undegraded material into lysosomes.[1] Although most LSDs result from acidic hydrolase deficiencies, a considerable number of these conditions result from defects in either membrane lysosomal proteins or in other non-lysosomal proteins that are critical for proper function of the lysosomal system. The incidence of LSDs is estimated to be approximately 1:5,000 live births, but the true figure is likely greater because of undiagnosed or misdiagnosed cases. The progressive lysosomal accumulation of undegraded metabolites results in lysosomal dysfunction and consequent generalised cell and tissue damage, and, ultimately, to multi-systemic pathology.[2] Storage may begin during early embryonic development, and the clinical presentation for LSDs can vary from an early and severe phenotype to late-onset mild disease. Relatively few LSDs lack pathology in the central nervous system (CNS). Indeed, in the majority of LSDs, CNS involvement is common (Table 1) and the consequent symptoms are often the most debilitating because neurodegeneration can occur in multiple brain regions (e.g., thalamus, cortex, hippocampus, and cerebellum). In the context of improving the life expectancy of people with LSDs, new research initiatives have been launched with the specific remit of elucidating how lysosomal dysfunction may specifically affect neuronal function and viability, thus determining the neuropathological phenotype observed in LSDs. In this article we discuss the most recent advances in these studies useful for developing possible therapeutic interventions.

## The Lysosome in normal cell physiology and diseases

Lysosomes are membrane-bound organelles with an acid lumen that contain several types of hydrolases that are responsible for the degradation of specific substrates. Lysosomal functions can be classified into three main types: degradation, secretion and signalling.[3] Lysosomes are involved in the degradation and recycling of extracellular material (via endocytosis) and intracellular material (via autophagy). Extracellular material reaches the lysosome generally by endocytosis through specific endocytic mechanisms based on the nature of the cargo. Intracellular materials reach the lysosome through autophagy, a catabolic pathway used by cells to capture cytoplasmic components for degradation and recycling.[4] Through autophagy, macromolecules and organelles are recycled via autophagosome-medi-

| LSD | DEFECTIVE ENZYME | NEUROLOGICAL FEATURES |
|---|---|---|
| **SPHINGOLIPIDOSES**<br>• **GM1 and GM2 gangliosidosis**<br>• **Niemann-Pick disease (NPC)**<br>• **Gaucher disease**<br>• **Others** | **Lysosomal hydrolases** (i.e. *Hexosaminase A* in GM2; *Sphingomyelinase* in NPC; *Glucocerebrosidase* in Gaucher disease) | Progressive neurological regression, seizures, spasticity, |
| **MUCOPOLYSACCHARIDOSES**<br>• **MPS-III**<br>• **Others** | **Glycosaminoglycan cleaving enzymes** | Mental retardation, behavioural disturbances and hyperactivity |
| **GLYCOPROTEINOSES**<br>• **Mucolipidosis**<br>• **Others** | **Glycoprotein cleaving enzymes** (*N-acetylglucosamine-1-phospotransferase* in Mucolipidosis-I ) | Mental impairment, speech impairment, spasticity, neuroaxonal dystrophy |
| **NEURONAL CEROID LIPOFUSCINOSIS**<br>• **Batten disease**<br>• **Others** | **Lysosomal proteins (e.g. proteases)** (i.e. *CLN3 in Batten)* | Visual failure, epilepsy, decline in motor and cognitive skills |
| **MULTIPLE SULFATASE DEFICIENCY** | **Sulfatase modifier** | Rapid neurological deterioration |

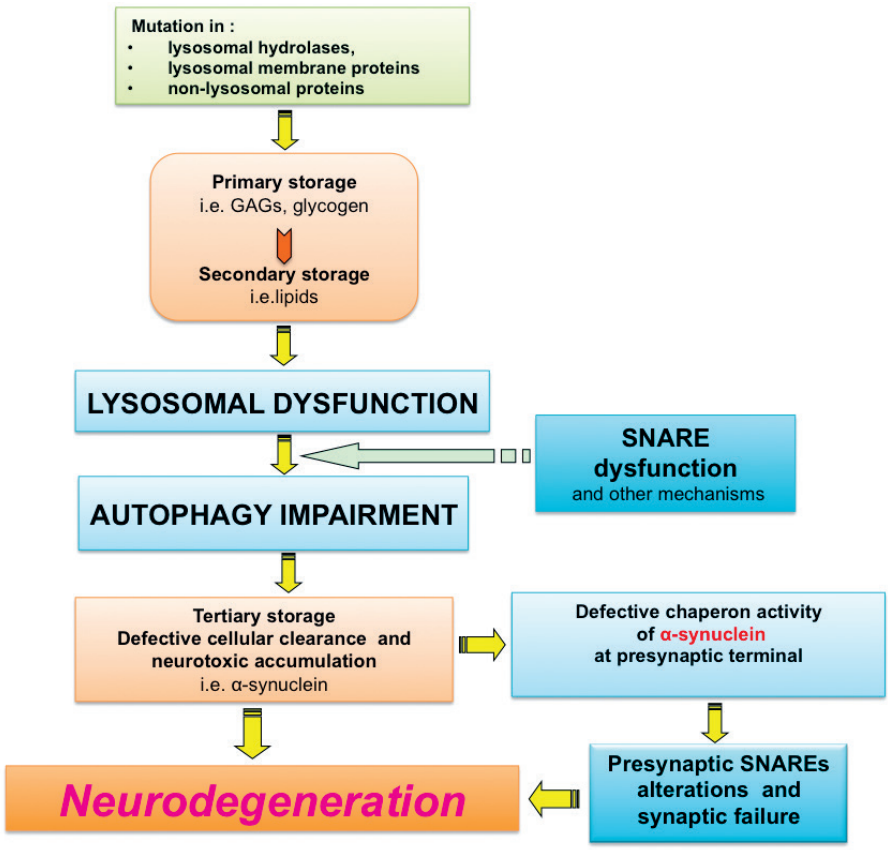


Figure 1. Mechanisms underlying lysosomal dysfunction in LSDs

The figure illustrates the main steps determining LSD neuropathogenesis. Mutations in genes, which are important for lysosomal degradation activity result in the lysosomal accumulation of specific un-degraded substrates (Primary storage). This leads to the accumulation of other lysosomal substrates (Secondary storage) due to the secondary inhibition of lysosomal degradation capacity. Lysosomal dysfunction is associated with autophagy impairment, due to the inefficient fusion between lysosomes and autophagosomes. Defective function of SNARE proteins has also been associated with lysosomal fusion defects. Autophagy stress causes tertiary storage of dysfunctional organelles and neurotoxic molecules (e.g., α-synuclein). α-Synuclein accumulation may contribute to neurodegeneration through interacting with presynaptic SNARE proteins leading to synaptic failure through the defective chaperone activity of this protein at the presynaptic nerve terminals.

ated transport to, and fusion with, lysosomes. The resulting breakdown products are used to generate new cellular components and energy in response to the nutritional needs of the cell. Lysosomes also undergo $Ca^{2+}$ regulated exocytosis to secrete their content into the extracellular space and to repair damaged plasma membranes.[5] Lysosomal exocytosis may also directly modulate cellular clearance.[6] More recently, lysosomes have been identified as signalling organelles that can sense nutrient availability and activate a lysosome-to-nucleus signalling pathway that mediates the starvation response and regulates energy metabolism.[7] The importance of proper lysosomal function to normal cell physiology is highlighted by the fact that lysosomal dysfunction initiates degenerative processes in a number of human diseases and is also involved in the process of ageing[8] (Figure 1).

Lysosomal dysfunction has been associated with neuropathology not only in LSDs but also in the most common forms of neurodegenerative disorders such as Parkinson's, Huntington's and Alzheimer's diseases.[9]

In Huntington's disease the aggregate-prone proteins huntingtin (HTT) may affect the efficiency of autophagy by inhibiting cargo recognition by autophagosomes.[10]

Patients with Alzheimer's disease carrying mutations in presenilin 1 (PSEN1) showed lysosomal and autophagic dysfunction.[11] Lysosome dysfunction in these patients can be explained by two different mechanisms, one involving a defect in the lysosomal acidification machinery and the other a defect in lysosomal $Ca^{+2}$ homeostasis.[12]

Another aggregate-prone protein, α-synuclein, forms intra-neuronal inclusions called Lewy bodies in Parkinson's disease (PD). A significant number of patients with Parkinson's disease are heterozygous for mutations in the gene encoding the lysosomal enzyme β-glucocerebrosidase (GBA) – which when present as homozygous mutations cause Gaucher's disease, a neurodegenerative LSD. It has been shown that lower levels of GBA lead to an increased accumulation of glucosylceramide in the lysosome, that in turn accelerates the synthesis of soluble α-synuclein oligomers that eventually are converted into amyloid fibrils.[13] Furthermore, the accumulation of α-synuclein also blocks the trafficking of newly synthesised GBA to the lysosome and thus further amplifies glucosylceramide accumulation.[14] All of these findings indicate that if α-synuclein can somehow be cleared, alpha-synucleinopathies can be prevented or even reversed. An interesting example has emerged recently from the work of McNeil and colleagues[30] in which they demonstrated that a commercial drug called "ambroxol", is able to increase the amount of the enzyme GBA. These results strongly suggest that ambroxol hydrochloride should be further investigated as a potential treatment for PD and α-synuclein-dependent neuropathologies such as LSDs.

In addition, mutations in ATPase type 13A2 (ATP13A2), a component of the lysosomal acidification machinery, has also been found in patients with hereditary parkinsonism and are associated with lysosomal dysfunction, defective clearance of autophagosomes and accumulation of α-synuclein.[15] Furthermore, mutations in the genes encoding PINK (PTEN-induced putative kinase) and PARKIN (Parkinson's disease protein) are associated with the defective clearance of mitochondria, leading to Parkinson's disease.[16] Finally there are also some Parkinson's disease patients with VPS35 (vacuolar protein sorting 35) mutations, which encodes for an endosomal protein involved in the retrograde transport between endosomes and the trans-Golgi network.[17]

**Neurodegenerative mechanisms in LSDs**

The prominent pathological hallmark of LSDs is a severe neurodegeneration, which is connected to lysosome dysfunction. A variety of lysosomal-dependent pathogenic cascades are activated in LSDs, such as impaired autophagic flux, altered calcium homeostasis, oxidative stress, inflammation, altered lipid trafficking, endoplasmic reticulum stress and autoimmune responses. The mechanisms linking these pathogenic cascades to lysosomal dysfunction are now being better understood.[18,19,20] The impairment of autophagy plays an important role in the pathogenesis of LSDs.[21] In neurons the failure of autophagy results in secondary accumulation of toxic substrates, aggregate-prone proteins and damaged organelles. Toxic storage triggers neurodegenerative processes since it is a critical determinant of cell death in post-mitotic cells such as neurons. Indeed, intact autophagic pathways are crucial to maintain normal neuronal function[22] and any decline of their degradation capability contributes to the pathogenesis not only of LSDs but also to age-related neurodegenerative disorders.[23] A critical mechanism underlying lysosomal dysfunction and autophagic impairment in LSDs involves soluble NSF attachment receptor (SNARE) proteins. SNAREs are a group of proteins which are responsible for mediating membrane fusion processes in cells. By studying two neurodegenerative LSDs, the mucopolysaccharidosis type IIIA (MPS-IIIA) and Multiple Sulfatase Deficiency (MSD), it has been demonstrated that cholesterol accumulation in lysosomal membranes impairs SNARE function thus leading to defective fusion of lysosomes with target membranes including autophagosomes.[24] Furthermore SNARE impairment has been identified as an important mechanism underlying lysosomal dysfunction and autophagic defects in NPC-1[25] as well.

An additional pathogenic process that has recently been put forward is based on the fact that α-synuclein accumulation has been found in a number of LSDs (ref: Chachar et al Movement Disorders, 2011). Moreover, patients heterozygous for GBA mutations can develop PD with its alpha synuclein Lewy bodies. Now exactly how α-synuclein accumulation and aggregation mediates neurotoxicity remains still unclear but recently, α-synuclein has been identified as a key chaperone protein assisting synaptic vesicle recycling and transmission at presynaptic terminals. Specifically, α-synuclein ensures the proper function of synaptic SNARE proteins, which represent the key component of the neuronal cellular fusion machinery at nerve terminals.[31,32] This evidence raises the intriguing hypothesis that lysosomal-dependent α-synuclein accumulation found in LSDs may contribute to trigger neurodegeneration in these pathologies by causing α-synuclein chaperone deficits and presynaptic failure. This may represent a new mechanistic link between lysosomal dysfunction and neuronal degeneration in LSDs (Figure 1).

In conclusion, understanding how the failure of the lysosomal system impacts on neuropathology in LSDs may uncover new pathogenic cascades and through this new therapeutic agents. Moreover, by studying neuropathogenic mechanisms in LSDs this may help clarify not only the cell biology of lysosomal diseases but the much more common age-related neurodegenerative disorders.

REFERENCES


1. K, S. *Lysosomal disease.* In Greenfield's Neuropathology, Graham DI, Lantos PL (eds) 653–735(2002).
2. Ballabio, A. & Gieselmann, V. *Lysosomal disorders: from storage to cellular damage.* Biochim Biophys Acta 1793, 684-696 (2009).
3. Settembre C, Fraldi A, Medina DL & Ballabio A. *Signals from the lysosome: a control centre for cellular clearance and energy metabolism.* Nat Rev Mol Cell Biol 2013;14:283-96.
4. Mizushima N. *Autophagy: process and function.* Genes & development 2007;21:2861-73.
5. Andrews NW, Almeida PE & Corrotte M. *Damage control: cellular mechanisms of plasma membrane repair.* Trends in cell biology (2014).
6. Medina DL, et al. *Transcriptional activation of lysosomal exocytosis promotes cellular clearance.* Developmental cell 2011;21:421-30.
7. Settembre C, et al. *A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB.* The EMBO journal 2012;31:1095-108.
8. Cuervo AM & Dice JF. *When lysosomes get old.* Experimental gerontology 2000;35:119-31.
9. Nixon RA, Yang DS & Lee JH. *Neurodegenerative lysosomal disorders: a continuum from development to late age.* Autophagy 2008;4:590-9.
10. Jeong H, et al. *Acetylation targets mutant huntingtin to autophagosomes for degradation.* Cell 2009;137:60-72.
11. Lee JH. et al. *Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations.* Cell 2010;141:1146-58.
12. Coen K, et al. *Lysosomal calcium homeostasis defects, not proton pump defects, cause endo-lysosomal dysfunction in PSEN-deficient cells.* The Journal of cell biology 2012;198:23-35.
13. Sidransky E, et al. *Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease.* The New England journal of medicine 2009;361:1651-61.
14. Mazzulli JR, et al. *Gaucher disease glucocerebrosidase and alpha-synuclein form a bidirectional pathogenic loop in synucleinopathies.* Cell 2011;146:37-52.
15. Ramirez A, et al. *Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase.* Nature genetics 2006;38:1184-91.
16. Geisler S, et al. *PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1.* Nature cell biology 2010;12:119-31.
17. Zimprich A, et al. *A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease.* American journal of human genetics 2011;89:168-75.
18. Schultz ML, Tecedor L, Chang M & Davidson BL. *Clarifying lysosomal storage diseases.* Trends in neurosciences 2011;34:401-10.
19. Platt FM, Boland B & van der Spoel AC. *The cell biology of disease: lysosomal storage disorders: the cellular impact of lysosomal dysfunction.* The Journal of cell biology 2012;199:723-34.
20. Vitner EB, Platt FM & Futerman AH. *Common and uncommon pathogenic cascades in lysosomal storage diseases.* The Journal of biological chemistry 2010;285:20423-7.
21. Settembre C, Fraldi A, Rubinsztein DC & Ballabio A. *Lysosomal storage diseases as disorders of autophagy.* Autophagy 2008;4:113-14.
22. Komatsu M, et al. *Loss of autophagy in the central nervous system causes neurodegeneration in mice.* Nature 2006;441:880-4.
23. Harris H & Rubinsztein DC. *Control of autophagy as a therapy for neurodegenerative disease.* Nature reviews. Neurology 2012;8:108-17.
24. Fraldi A, et al. *Lysosomal fusion and SNARE function are impaired by cholesterol accumulation in lysosomal storage disorders.* The EMBO journal 2010;29:3607-20.
25. Sarkar S, et al. *Impaired autophagy in the lipid-storage disorder Niemann-Pick type C1 disease.* Cell reports 2013;5:1302-15.
26. Spillantini MG & Goedert M. *The alpha-synucleinopathies: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy.* Annals of the New York Academy of Sciences 2000;920:16-27.
27. Bendor JT, Logan TP & Edwards RH. *The function of alpha-synuclein.* Neuron 2013;79:1044-66.
28. Bourdenx M, Bezard E & Dehay B. *Lysosomes and alpha-synuclein form a dangerous duet leading to neuronal cell death.* Frontiers in neuroanatomy 2014;8:83.
29. Xu YH, et al. *Accumulation and distribution of alpha-synuclein and ubiquitin in the CNS of Gaucher disease mouse models.* Molecular genetics and metabolism 2011;102:436-47.
30. McNeill A, et al. *Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells.* Brain: a journal of neurology 2014;137:1481-95.
31. Burgoyne RD & Morgan A. *Chaperoning the SNAREs: a role in preventing neurodegeneration?* Nature cell biology 2011;13:8-9.
32. Burre J, et al. *Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro.* Science 2010;329:1663-7.

# Sir William Gowers (1845-1915): a centenary celebration, with an examination of his comments on cognitive dysfunction

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2015 marks the 100th anniversary of the death of Sir William Gowers (Figure), one of the towering figures of clinical neurology in the late 19th and early 20th centuries, who has rightly entered the pantheon of neurological greats.[1,2] A splendid recent biography has provided many insights into his life and career.[3]

Gowers' neurological contributions are manifold. Most, if not all, neurologists will be familiar with Gowers' sign or manoeuvre observed in patients with proximal lower limb and trunk weakness as they attempt to rise from the ground, a sign also known as "climbing up oneself" or, in North America, as the "butt-first manoeuver", most typically seen in boys with Duchenne muscular dystrophy, a disorder which Gowers knew as pseudohypertrophic muscular paralysis and on which he wrote a monograph. Those familiar with the anatomy of the spinal cord will know of Gowers' tract (ventral or anterior spinocerebellar tract).

Gowers was a fecund and lucid writer, author of many publications, both papers (more than 300) and books (Box), which culminated in the *Manual of Diseases of the Nervous System*. This book has been variously described as "the greatest single-author comprehensive textbook of clinical neurology ever published" (Ref 3, p. 250) and as the "Bible of Neurology",[4] and is perhaps Gowers' most enduring monument. Its two volumes first appeared in 1886 ("Diseases of the nerves and spinal cord") and 1888 ("Diseases of the brain and cranial nerves. General and functional diseases of the nervous system"), with a second edition in 1892 (Volume 1) and 1893 (Volume 2). A third edition of volume 1 appeared in 1899, co-authored with Dr James Taylor, but although preparations for a third edition of volume 2 were made this was never published. Parts of a manuscript marked with Gowers' proposed corrections survive in the Queen Square archives (Ref 3, p. 149), with new information particularly relating to nystagmus and myasthenia.[4]

Gowers' neurological interests were very broad, but perhaps particularly related to epilepsy,[5] syphilis (especially tabes and locomotor ataxy), movement disorders, including "paralysis agitans" (Parkinson's disease) and "scrivener's palsy" (writer's cramp), and migraine. The student of cognitive neurology is disappointed to learn from his biographers that "from a survey of all Gowers' publications one gains the impression that he was not particularly interested in higher cerebral function" (Ref 3, p. 167), presumably because many of the conditions afflicting these faculties were at that time seen by "alienists" (psychiatrists) rather than neurologists. That said, he evidently took an interest in his own powers of recollection, which were said to be remarkable (Ref 3, p. 238), although perhaps not unexpectedly tailed off in his later years.[6]

Prompted by the biography suggestion of lack of interest in cognitive neurology, I visited the Liverpool Medical Institution which holds copies of all the editions of the *Manual of Diseases of the Nervous System* (see www.lmi.org.uk and follow the link to Online Library Catalogue). I have examined these volumes, in particular the second edition of volume 2 of 1893, in order to try to gain some appreciation of Gowers' knowledge of and approach to what we might now define as cognitive disorders (unless otherwise stated, all subsequent page citations are to the 1893 edition of the *Manual*, volume 2, although I wish to emphasise that, since I have not read all the 1050 pages of text in the LMI copy, this does not purport to be a comprehensive account).

A brief perusal is initially discouraging: for example, there is no index entry for "dementia", although it is evident that this word was certainly part of Gowers' clinical vocabulary since he does use it on occasion (e.g. pp. 107, 648, 983). Much of what we call "dementia" is probably subsumed in his categories of "mental failure" and "insanity". It is clear that Gowers was familiar with many of the symptoms of cognitive dysfunction, and many of the disorders causing such problems.

## Cognitive symptoms

### *Amnesia*

In describing "Mental symptoms" (98), Gowers noted that "mental functions of the brain are frequently disturbed in organic disease", and that "Simple mental failure is indicated first and chiefly by *defect of memory*, 'amnesia' in the widest sense of the word" (Gowers' italics; 107). Hence, "The diseases of the brain that affect memory are extremely numerous", including "various degenerative processes, which are for the most part classed as forms of insanity, e.g. senile dementia and general paralysis of the insane" (107). Under the heading of "Mental failure", the index includes references to epilepsy, chorea, and tumour, amongst others (1060).

### *Aphasia*

It has been acknowledged that the *Manual* contains a very good account of aphasia (Ref 3, p. 167). Gowers noted of cerebral defects of speech that "The subject abounds in difficulty" (111). Amongst the most important writings on the subject, Gowers cited Broca (111n), Wernicke (109n), and Hughlings Jackson (109n, "in many places, but especially in 'Brain' vols. i and ii").

Gowers drew a clear distinction between motor aphasia (116-119) in which the "patient is able to understand whatever is said to him" despite impaired speech output, and sensory aphasia (119-122) in which "heard words are not understood". He seems to have used the term "word deafness" interchangeably with "sensory aphasia". The defects of writing (agraphia) and reading (alexia) accompanying these two forms of aphasia are also described.

REFERENCES

1. Tyler KL. *William Richard Gowers (1845-1915).* J Neurol 2003;250:1012-1013.
2. Rose FC. *History of British neurology.* London: Imperial College Press, 2012:130-137.
3. Scott A, Eadie M, Lees A. *William Richard Gowers 1845-1915. Exploring the Victorian brain: a biography.* Oxford: Oxford University Press, 2012.
4. Eadie MJ, Scott AE, Lees AJ, Woodward M. *William Gowers: the never completed third edition of the "Bible of Neurology".* Brain 2012;135:3178-3188.
5. Shorvon S, Shepherd L. *The beginning of the end of the falling sickness. Epilepsy and its treatment in London 1860-1910.* London, 2012:30-32.
6. Sacks O. *Gowers' memory.* Neurology 1996;46:1467-1469.
7. Larner AJ, Gardner-Thorpe C. *Robert Lawson (?1846-1896).* J Neurol 2012;259:792-793.
8. Larner AJ. *Solomon Carter Fuller (1872-1953) and the early history of Alzheimer's disease.* Adv Clin Neurosci Rehabil 2013;12(6):21-22.

As regards causation of aphasia, "The region of the cortex in which the speech-centres are situated is supplied by the middle cerebral artery…, and obstruction of this is the most frequent cause of aphasia" (124). Transient aphasia in the context of right-sided convulsions and of migraine is also noted (124).

***"Agnosia"***

As far as I can see, Gowers does not use the word "agnosia", coined by Freud in 1891, but he was clearly aware of what we would now regard as agnosic phenomena, which 19th century neurologists had called "imperception" or "asymbolia".

He described "word-blindness" as an isolated loss of the power of comprehending visual word-symbols, after Kussmaul, with an inability to read even simple words (122). He noted that such patients could write spontaneously or from dictation but could not copy (123) and that there may be an associated hemianopia (124). Hence this corresponds with what we might now call pure alexia, alexia without agraphia, or pure word blindness. Gowers thought this resulted from a lesion in the lower and hinder part of the left parietal lobe including the angular gyrus. He also characterised word-blindness as a partial form of "mind-blindness", after Munk, that being impaired power to recognise the nature of seen objects, including words, although they could be "recognised at once when some other sense is employed" (23). Gowers' possible role in defining the pathological substrate of one of Hughlings Jackson's patients with agnosia has been described (Ref 3, p. 167).

**Cognitive disorders**

***Senile amnesia, Senile dementia***

Gowers reported, in a section headed "Senile atrophy" (581-582), that "In old age the brain wastes, like many other organs ... The amount of fluid in the ventricles and on the surface is increased in proportion to the lessened bulk of the brain ... this wasting of the brain is commonly attended by no symptoms. Senile mental failure is often ascribed to it, but ... caution should be observed in attributing to it any mental change that may co-exist". He recognised "senile dementia" as a condition, and a temporal gradient in "senile amnesia", in which "... the events of early life may be vividly remembered, and those of later years be lost" (107).

***Paralysis agitans***

In his descriptions of what we would now call Parkinson's disease, Gowers noted that the "intellect may be unaffected throughout", as per James Parkinson's original 1817 description of the disease, but noted that "in the later stages of the disease ... mental weakness and loss of memory" are occasionally present and that these might also occur early in the disease course (648). "If tremor is inconspicuous, they add considerably to the misleading aspect of the case. Very rarely they are accompanied by a tendency to delusions, and occasionally

they amount to actual dementia" (648). One wonders in retrospect if Gowers is describing what we might call dementia with Lewy bodies here.

***Hereditary chorea, Huntington's chorea***

Gowers noted that George Huntington's original 1872 description of this disorder mentioned "mental failure" as one aspect of the disease (624). Gowers' own focus was principally on the chorea, but he did note that "Mental changes are generally associated, especially mental weakness, and hence many of the cases have been reported from asylums" (625).

***Epilepsy***

In the section on "Mental disturbance in Epileptics" (747-749), Gowers noted that the "interparoxysmal mental state of epileptics ... often presents grave deterioration ... In its slightest degree there is merely defective memory, especially for recent acquisitions. In greater degree the intellect suffers generally ... " (748). Furthermore, "The mental state is not, in all cases, entirely the result of the attacks of epilepsy. In some it is, in part at least, the expression of a cerebral imperfection, of which the epilepsy is another manifestation. In such instances mental defect may exist before the occurrence of the first fit" (748). Certainly there is some modern evidence corroborating this formulation.

The possible adverse cognitive effects of medication, specifically bromides, of which Gowers was an enthusiastic prescriber,[5] are noted: "… patients may become ... forgetful ... The effect is often ascribed to the remedy used, especially if this is bromide" (749).

***Disseminated or insular sclerosis***

In disseminated or insular sclerosis (multiple sclerosis), Gowers noted that "slight mental change is common; considerable alteration is very rare. … There may be failure of memory, but especially frequent is an undue complacency and contentment" (552).

***Alcohol***

Describing the effects of "Chronic alcoholism", Gowers noted that "persistent mental changes" such as "failure of memory" might occur (981). "Chronic alcoholism may aid in the production of many forms of definite insanity, but the only variety that can be certainly ascribed to this cause, acting alone, is chronic dementia – failure of memory, commonly progressive for a time" (983). He noted a resemblance to general paralysis of the insane but "differing in the non-progressive character of the disorder if alcohol is given up". He makes no reference as far as I can see to the alcohol-related amnesic syndrome described by Korsakoff in 1887, or the earlier work of Robert Lawson which had appeared in the inaugural volume of *Brain* in 1878.[7]

***Syphilis***

Although Gowers' major interest related to tabes and locomotor ataxy, he was aware that this might co-exist with general paralysis of the insane, and noted that "syphilis predisposes to both" (1892 edition of *Manual*, volume 1, p. 417).

**Discussion**

Evidently, from a brief perusal of some parts of his *Manual*, Gowers was familiar with the symptoms of cognitive dysfunction and with disorders of the nervous system causing such dysfunction. This reflects his astute clinical skills. His comments on cognitive impairment in Parkinson's disease may be prescient, and certainly the cognitive impairments he noted in multiple sclerosis and epilepsy were relatively little studied until recent times. Lacking specific tools to assess cognitive function, the development of which was in its infancy, he could not really take these clinical observations much further.

It is intriguing to wonder what new information relevant to cognitive disorders might have been contained in the 3rd edition of volume 2 of the *Manual*. "Brain degenerations" is apparently one of the surviving sections of the proposed third edition of volume 2, with Gowers' handwritten revisions, although Eadie et al. state that in this section "deletions were trivial" (Ref 4, p. 3180). It would be fascinating to know if this section mentioned the seminal publications of Arnold Pick on focal lobar degenerations of 1892 and 1906 (Gowers had learnt German), and likewise those of Alois Alzheimer of 1907 and 1911, although it was not until 1912 that the first publication on "Alzheimer's disease" in English appeared, by Solomon Carter Fuller,[8] by which time Gowers had ceased to publish.

**Box: Major books published by Sir William Gowers**

*A Manual and Atlas of Medical Ophthalmoscopy*
*Pseudo-hypertrophic Muscular Paralysis*
*The Diagnosis of Diseases of the Spinal Cord*
*Manual of Diseases of the Nervous System*
*Syphilis of the Nervous System*
*Epilepsy and Other Chronic Convulsive Disorders*
*The Border-land of Epilepsy: Faints, Vagal Attacks, Vertigo, Migraine, Sleep Symptoms and their Treatment*

# Buckets More MND Research


The MND Ice Bucket Challenge raised £7 million for the Motor Neurone Disease Association last summer. It was a global social media phenomenon that we couldn't have predicted but has had a massive impact. On 12 February, we celebrated this unexpected windfall and shared how the money will be spent.[1] The decisions on where the funding will be allocated were informed by a consultation with our members (over 2,000 of them responded).

£5m of the Ice Bucket Challenge funds has been allocated to MND research. Our plans to create an induced pluripotent stem cell bank from patients with MND will be realised sooner. In addition we now have the funds to analyse all our DNA bank samples by whole genome sequencing (WGS) as part of an international MND collaboration called Project MINE.

Genetics remains a fruitful and critical area to invest in. But the recent announcement that TBK1 is a genetic susceptibility gene for MND, from a study of 2,874 samples from patients with the sporadic form of MND across the world[2] illustrates the complexity of the genetic contribution to the cause of MND. In approximately 5-10% of people with MND, there is a family history of the disease. For the remaining 90-95% of people, the disease is apparently sporadic, nevertheless, there is still a strong genetic contribution. For many years, mutations in the superoxide dismutase 1 gene (SOD1), found in 20% of those with a family history, were the only thing that we knew about the genetic cause of this devastating condition. From the mid-2000s onwards the pace of genetic discovery accelerated and a string of MND-causative genes were found. One highlight, in 2011, was the discovery of a hexanucleotide repeat expansion in MND and also in frontotemporal dementia (C9orf72), providing a common biological link between the two diseases. The current tally means that approximately 65% of all cases of familial MND are attributed to known genetic mutations.[3]

These advances have been made on the cusp of the era of 'next generation' sequencing. As the last decade revealed so much, we have high hopes of the advances in knowledge that the next era of genetic analysis will bring.

The Ice Bucket Challenge windfall allows us to speed up our ambition of conducting WGS on all the patient samples within the UK MND DNA Bank, rather than one subset of samples at a time, as originally planned. These 1,700 samples will be added to a target WGS analysis of 15,000 samples from people with MND across the world. The target has been set by the Netherlands-led international consortium WGS project, Project MINE.[4] This large number of samples will provide more robust results – and a consortium approach will help in analysing the staggering amount of data generated. Our aim is to identify more causative genes of the inherited form of MND and greatly increase our understanding of the genetic contribution to all forms of the condition.

Aside from genetic research, another exciting Ice Bucket Challenge legacy is to expedite the development of an induced pluripotent stem cell (iPSC) bank from patients with MND. iPSCs will be created from patient and control lymphoblastoid cell lines, that form part of the UK MND DNA Bank. The Bank contains DNA and cell lines from people with MND, family members and spouse controls. The MND Association funded the creation of the bank and continues to act as its custodian.[5]

Researchers will be able to use this quality assured, well-phenotyped iPSC bank to derive motor neurons and glia for studies in the lab. Alterations in the molecular cell biology of motor neurons and glia from patients with MND will be compared to those from unaffected controls. Ultimately we hope that therapeutic targets will be identified and the same derived cells can then be used to test drugs modifying these targets.

These research ambitions are exciting, but they will take years to realise. In the interim, the MND Association is committed to supporting people with MND and their families currently living with this devastating condition.

MND is a rare disease, with a worldwide prevalence of 5 - 7 per 100,000,[6] so for people living with MND, the increased awareness of MND created by the Ice Bucket Challenge was equally important as the hard cash. Some of the Ice Bucket Challenge money will be used to maintain public awareness. We are also working to raise awareness of the needs of people with MND with medical and healthcare communities: building partnerships to provide education and support. For example, a joint MND Association and Royal Society of Medicine study day on 'Recent Studies and the Diagnosis of MND' takes place in Liverpool on 6 May 2015 (see the advert on the inside front cover of this issue).

For updates on MND Association activities and specifically the latest news on MND research please see our website www.mndassociation.org and follow us on social media: www.facebook.com/mndassociation @mndassoc and @mndresearch accounts on Twitter.

mnda motor neurone disease association

References

1. Ice Bucket Challenge funding announced www.mndassociation.org/IBCmoney
2. Cirulli et al Science 2015 DOI: 10.1126/science.aaa3650
3. Renton et al. Nature Neuroscience 2014;17:17-23.
4. Project MINE website: https://www.projectmine.com/
5. Website of the UK MND DNA Bank: www.mndassociation.org/dnabank
6. Abhinav et al Neuroepidemiology 2007;29:44-48.

# Consensus meeting on the use of perampanel▼ as adjunctive therapy in clinical practice: recommendations from an expert panel

Special Feature 2015


## Summary

Perampanel has a novel mode of action based on a rational hypothesis of seizure initiation and spread. This can be considered when discussing the possibility of initiating perampanel treatment in patients with partial onset seizures who have failed to gain control with other AEDs.

Perampanel is an easy to use antiepileptic treatment that, based on the results of phase 3 placebo-controlled studies, has an efficacy profile comparable to other recently-introduced treatments. Currently-available data demonstrate a reduction of secondarily generalised seizures with perampanel treatment.

Data from 'real-world' studies and clinical experience support the evidence from randomised controlled studies and confirm that perampanel is effective and generally well tolerated in clinical practice. No new safety signals or concerns have emerged to date.

All patients with refractory partial-onset seizures should be reviewed by an epilepsy specialist when possible. Perampanel may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Ongoing perampanel prescribing may be undertaken in primary care with support from a consultant neurologist or epilepsy nurse specialist if required. Perampanel can be considered a 2nd-line adjunctive therapy option in patients aged 12 years and older with partial-onset seizures.

Perampanel may be combined with other AEDs with good efficacy outcomes. A higher dose of perampanel may be required in patients taking enzyme-inducing AEDs.

Perampanel should be initiated at a dose of 2 mg/ day, taken at bedtime, and titrated by increments of 2 mg every 4 weeks according to clinical need to achieve the maximum tolerated dose (MTD) (up to 12 mg/day). Consider withdrawing perampanel if there is no evidence of clinical benefit once the MTD has been reached.


**For full prescribing information please refer to the summary of product characteristics.**

### Introduction

Perampanel (Fycompa®, Eisai Ltd.) is a first-in-class antiepileptic drug (AED) that was introduced into the UK in September 2012 for the adjunctive treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 12 years and older.[1] By November 2014, over 7500 patients had been treated with perampanel in the UK and Ireland.[2] In light of the increasing experience of using perampanel in clinical practice, a panel of epilepsy experts met in December 2014 to review their experiences of using the treatment and to develop consensus recommendations on its appropriate use in clinical practice. This report provides an overview of the latest clinical research findings with perampanel and summarises the group's feedback and consensus recommendations.

### Mode of action of perampanel

Perampanel is a selective, non-competitive antagonist of the ionotropic ∝-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) glutamate receptor on post-synaptic neurons.[1] These receptors are localised at excitatory synapses in the central nervous system, where they are essential for the generation and spread of epileptic activity.[3] Perampanel selectively and potently inhibits AMPA receptors and reduces neuronal hyperexcitability, demonstrating a broad-spectrum of activity in animal models used to identify AEDs.[4]

The group agreed that the novel and rational mode of action of perampanel was one of the considerations when developing an individual's treatment plan and discussing the possibility of initiating perampanel in relevant patients. For some patients, the novel mode of action of perampanel may be an attractive feature of the treatment that helps to explain the rationale for its use as an adjunctive AED.


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## Meeting Participants


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**Consensus statement 1:** Perampanel has a novel mode of action based on a rational hypothesis of seizure initiation and spread. This can be considered when discussing the possibility of initiating perampanel treatment in patients with partial onset seizures who have failed to gain control with other AEDs.

## Efficacy and safety of perampanel

The efficacy and safety of perampanel have been evaluated in a clinical development programme that included three phase 3, double-blind, placebo-controlled studies: study 304,[5] study 305[6] and study 306[7] and a recently-reported long-term extension study 307.[8] 1480 patients aged ≥12 years who were receiving one, two or three AEDs and experienced at least five partial-onset seizures during a 6-week baseline period were enrolled into the phase 3 studies. Perampanel doses of 2, 4, 8 and 12 mg taken once-daily were assessed. Doses were titrated up by 2 mg each week over a 6-week period, followed by a 13-week, double-blind maintenance phase. Primary efficacy endpoints were median % change from baseline in seizure frequency per 28 days and the percentage of patients achieving a ≥50% reduction in the frequency of all seizures per 28 days (50% responder rate; baseline versus maintenance).

*Pooled analysis of phase 3 studies*

This pooled analysis included data from 1480 patients who took part in the three phase 3 studies.[9] These were treatment-refractory patients who experienced a median of 10–13 partial-onset seizures per 28 days during the pre-randomisation phase of the studies, despite most individuals (86%) receiving two or three AEDs. The most common concomitant AEDs were carbamazepine, valproic acid, lamotrigine and levetiracetam. The key findings from this analysis are outlined below:[9]

**Efficacy:**

- Adjunctive therapy with perampanel 4, 8 and 12 mg/day significantly reduced the frequency of partial-onset seizures (Figure 1) and improved responder rates (Figure 2) compared with placebo.
- Perampanel 4,8 and 12 mg/day also significantly reduced the frequency of secondarily generalised seizures compared with placebo (Figure 3).
- At the recommended initial maintenance doses of 4–8 mg/day, up to 17% of patients achieved ≥75% reduction in seizure frequency.
- Seizure-freedom rates during maintenance therapy were higher with perampanel 4–12 mg/day (3.5–4.4%) than with placebo (1.0%) ($p<0.05$ for each dose, completer analysis).

**Safety and tolerability:**

- Perampanel was generally well tolerated. The most frequently-reported treatment-emergent adverse events (TEAEs) were dizziness and somnolence (Table 1).
- Psychiatric and behavioural TEAEs (e.g. irritability, hostility, aggression) were observed more frequently in perampanel-treated patients than in placebo-treated patients – the frequency of these events increased with increasing perampanel doses.
- Serious AEs were reported by a similar proportion of patients taking placebo (5.0%) and perampanel (5.5%).

This pooled analysis augments the findings from the individual studies demonstrating the efficacy and tolerability of perampanel as an adjunctive treatment for patients with partial-onset seizures. The group agreed that, in this highly treatment-refractory study population – which is typical of the populations now entering AED clinical trials – seizure freedom is not always a realistic goal. The efficacy profile of perampanel was considered by the group to be comparable to that of other recently-introduced AEDs.

*Long-term extension study*

Study 307 was designed as the long-term, open-label extension to the three phase 3 double-blind, placebo-controlled studies of adjunctive perampanel in partial-onset seizures to validate the initial registration study findings: 96% of eligible patients who completed the phase 3 trials entered this study.[8] The study was designed with a 16-week, blinded conversion period, during which all participants were up-titrated by 2 mg every 2 weeks to 12 mg/day or their maximum tolerated dose (MTD). This was followed by a long-term (~5 years) follow-up period during which dose adjustments of perampanel and concomitant AEDs could be made at the investigator's discretion.

At the time of latest reporting, 1216 patients had received perampanel for a median duration of 1.5 years (range 1 week to 3.3 years), with more than 300 patients having received treatment for >2 years.[8] The mean daily dose of perampanel achieved was 10.6 mg, with 92% of patients taking a maximum daily dose of 10 or 12 mg. Fifty-eight percent of patients were retained on perampanel treatment at the data cut-off point for this analysis. The key findings from this study were as follows:[8]

- Long-term adjunctive perampanel was generally well tolerated, with a safety and tolerability profile consistent with that reported in phase 2 and 3 studies.
- Most AEs reported were mild or moderate in intensity. The most frequently-reported

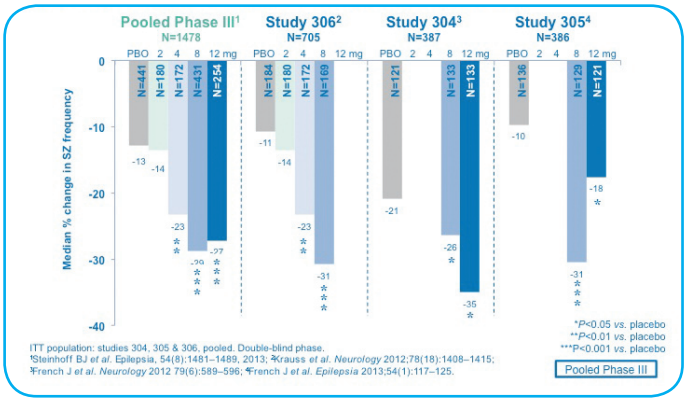


Figure 1. *Median percentage change in seizure frequency per 28 days reported in a pooled analysis of phase 3 studies[9] and individual studies[5–7] of adjunctive perampanel. Data shown are the differences between baseline and the double-blind treatment phase (ITT analysis set).*

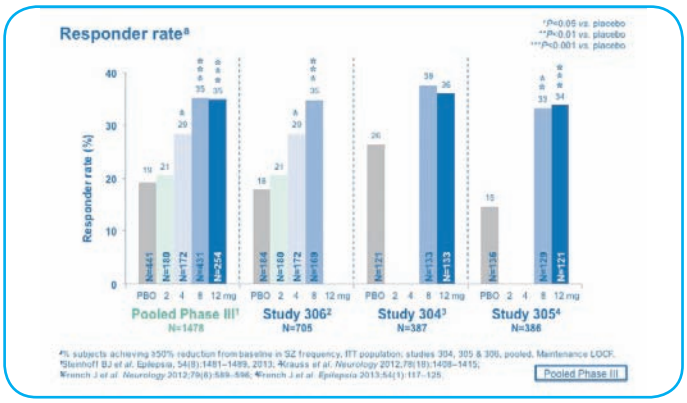


Figure 2. *Percentage of patients reporting a ≥50% reduction from baseline in seizure frequency in a pooled analysis of phase 3 studies[9] and individual studies[5–7] of adjunctive perampanel (ITT analysis set).*

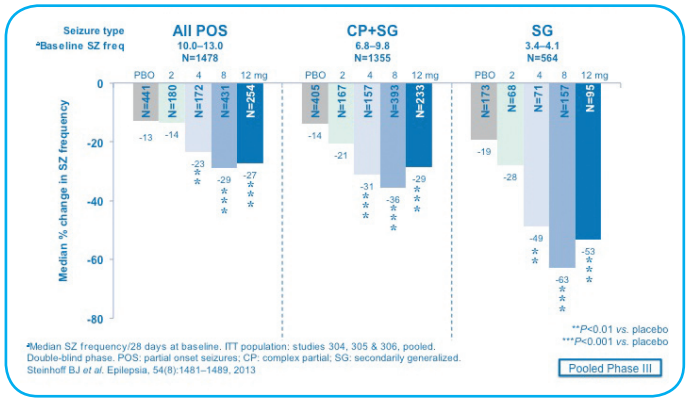


Figure 3. *Median percentage change in seizure frequency per 28 days according to seizure type in a pooled analysis of phase 3 studies of adjunctive perampanel.[9]*

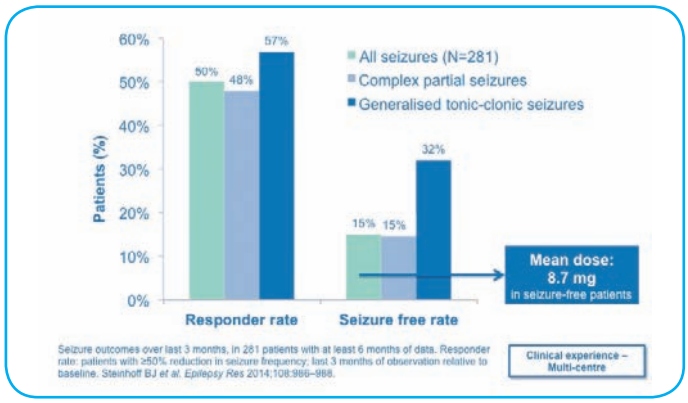


Figure 4. *Seizure outcomes in 'difficult-to-treat' patients receiving adjunctive perampanel in clinical practice: results of an observational study conducted in Austria and Germany.[10]*

adverse events were dizziness, somnolence, headache, fatigue, irritability and weight increase. Only dizziness and irritability led to treatment discontinuation in >1% of patients (3.9% and 1.3%, respectively).

- No new safety signals were observed with over 1803 patient-years of exposure to perampanel.
- Treatment efficacy in terms of seizure response was maintained over 2 years of perampanel treatment, indicating sustained benefits.
- Responder rates consistently remained above 40% after titration and reached 58% in the 337 patients treated for 2 years.
- In patients with secondarily generalised seizures at baseline, the frequency of these seizures was reduced by 77% at 9 months (n=422) and by 90% at 2 years (n=141).
- Long-term seizure freedom was achieved in some of these highly treatment-refractory patients (5% of patients treated for 1 year (n=694) and 3% of patients treated for 2 years (n=141)).

**Consensus statement 2:** Perampanel is an easy to use antiepileptic treatment that, based on the results of phase 3 placebo-controlled studies, has an efficacy profile comparable to other recently-introduced treatments. Currently-available data demonstrate a reduction of secondarily generalised seizures with perampanel treatment.

## Perampanel in the 'real-world': results from European and UK studies

Data are now emerging from 'real-world' observational studies conducted in clinical practice. One recently-reported study involved 281 'difficult-to-treat' patients with partial epilepsy being managed in epilepsy centres and neurology departments in Austria and Germany.[10] Data from consecutively-treated patients receiving adjunctive perampanel were collected for a minimum of 6 months. The mean dose of perampanel in this study was 7.7 mg/day.

After 6 months of follow-up, 169 patients (60%) were still receiving perampanel treatment and 43 patients (15%) had been seizure-free during the preceding 3 months at a mean dose of 8.7 mg/day (Figure 4). Half the patients had experienced at least a 50% reduction in their seizure frequency (all seizure types) (Figure 4). As in the phase 3 clinical trials, the most commonly reported AEs were somnolence and dizziness. Other AEs reported were ataxia, aggression, nausea and irritability.

The results from a number of other 'real-world' studies conducted in Spain,[11] the UK[12–19] and Ireland[20] have also been published or presented. These observational studies involving almost 500 patients who had taken adjunctive perampanel for up to 14 months in clinical practice confirm relatively high rates of treatment retention and good seizure response rates – typically at lower doses than were used in the controlled clinical trials. A seizure freedom rate of 17% was reported in one study.[13] In the view of the group the tolerability profile of perampanel in these 'real-world' studies reflected that observed in clinical trials, with dizziness, somnolence and irritability the most commonly-reported AEs.

The group reviewed their own experiences of using perampanel in clinical practice, reporting that the treatment is easy to use in a broad range of patients; it has a manageable tolerability profile and has been very effective in some patients. Cases were presented demonstrating sustained seizure-freedom in some previously intractable patients, early responses to perampanel treatment, frequent improvements in seizure severity, more rapid post-ictal recovery, and improved quality of life. Members of the group reported that, in some patients, it had been possible to reduce or withdraw other AEDs after initiation of perampanel treatment. Other cases were presented in which patients had a less favourable response, with an increase in irritability/aggression and/or mood disturbances leading to treatment withdrawal.

The panel members agreed that, in their experience, perampanel was generally well tolerated by most patients, with predictable early side-effects (e.g. dizziness), an acceptable neurocognitive profile, and manageable levels of headache and irritability. Treatment retention rates were reported to be generally high.

**Consensus statement 3:** Data from 'real-world' studies and clinical experience support the evidence from randomized controlled studies and confirm that perampanel is effective and generally well tolerated in clinical practice. No new safety signals or concerns have emerged to date.

## Optimising use of perampanel in clinical practice

Clinical guidelines from the National Institute for Health and Clinical Excellence (NICE) relating to the diagnosis and treatment of epilepsy were published in January 2012[21] and do not, therefore, include recommendations for the adjunctive use of perampanel in partial-onset seizures. The guidelines currently recommend that all patients with newly diagnosed partial-onset seizures are offered monotherapy with carbamazepine or lamotrigine as a first-line treatment (Table 1).[21] Alternative monotherapies for patients in whom these treatments are unsuitable or not tolerated are levetiracetam, oxcarbazepine and sodium valproate.[21] NICE-recommended adjunctive treatments are shown in Table 1. The NICE guidelines recommend that if standard adjunctive treatment is ineffective or not tolerated, advice should be sought from a tertiary epilepsy specialist.

*When to consider initiating perampanel*

There are currently no clear-cut, evidence-based guidelines to assist in the selection and sequencing of AED treatment. Treatment decisions are made empirically based on the seizure type and/or syndrome, the patient's age and gender, comorbidities and learning status, the side-effect profile of the drug, personal preferences, cost and affordability. The group agreed that, based on its ease of use and efficacy and tolerability profile, perampanel could be considered a 2nd-line adjunctive therapy option in patients with partial-onset seizures (Table 1). The group recommended that perampanel may be considered before pregabalin, gabapentin, tiagabine, phenytoin, phenobarbital, vigabatrin and retigabine in most patients. There are currently no specific predictive factors for the efficacy and tolerability of perampanel treatment – patients aged 12 years and older whose partial seizures are uncontrolled on monotherapy could therefore be potential candidates to receive adjunctive perampanel.

In-line with NICE guidance, the meeting participants concurred that all patients with refractory partial-onset seizures should be reviewed by an epilepsy specialist when possible. They agreed that perampanel may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Ongoing perampanel prescribing may be undertaken in primary care with support from a consultant neurologist or epilepsy nurse specialist if required.

**Consensus statement 4:** All patients with refractory partial-onset seizures should be reviewed by an epilepsy specialist when possible. Perampanel may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Ongoing perampanel prescribing may be undertaken in primary care with support from a consultant neurologist or epilepsy nurse specialist if required. Perampanel can be considered a 2nd-line adjunctive therapy option in patients aged 12 years and older with partial-onset seizures.

| | | Perampanel | | | |
|---|---|---|---|---|---|
| **Adverse event, n (%)** | **Placebo (n=442)** | **2 mg/day (n=180)** | **4 mg/day (n=172)** | **8 mg/day (n=431)** | **12 mg/day (n=255)** |
| Any TEAE | 294 (67%) | 111 (62%) | 111 (65%) | 350 (81%) | 227 (89%) |
| Dizziness | 40 (9%) | 18 (10%) | 28 (16%) | 137 (32%) | 109 (43%) |
| Somnolence | 32 (7%) | 22 (12%) | 16 (9%) | 67 (16%) | 45 (18%) |
| Headache | 50 (11%) | 16 (9%) | 19 (11%) | 49 (11%) | 34 (13%) |
| Fatigue | 21 (5%) | 8 (4%) | 13 (8%) | 36 (8%) | 31 (12%) |
| Irritability | 13 (3%) | 7 (4%) | 7 (4%) | 29 (7%) | 30 (12%) |
| Nausea | 20 (5%) | 4 (2%) | 5 (3%) | 25 (6%) | 20 (8%) |
| Fall | 15 (3%) | 2 (1%) | 3 (2%) | 22 (5%) | 26 (10%) |
| Nasopharyngitis | 18 (4%) | 7 (4%) | 9 (5%) | 23 (5%) | 11 (4%) |
| Upper RTI | 12 (3%) | 11 (6%) | 6 (4%) | 14 (3%) | 10 (4%) |
| Ataxia | 0 | 0 | 1 (<1%) | 14 (3%) | 21 (8%) |
| Balance disorder | 2 (<1%) | 0 | 0 | 22 (5%) | 8 (3%) |

TEAE, treatment-emergent adverse event; RTI, respiratory tract infection

Table 1. *Treatment-emergent adverse events reported in ≥5% of patients in any treatment group: results from a pooled analysis of phase 3 studies*[9]

| **1st-line monotherapy** (NICE guidelines) | **2nd-line monotherapy** (NICE guidelines) | **1st-line adjunctive therapy** (NICE guidelines) | **2nd-line adjunctive therapy** (Consensus meeting participants) | **3rd-line adjunctive therapy** (Consensus meeting participants) |
|---|---|---|---|---|
| Carbamazepine<br>Lamotrigine | Carbamazepine<br>Lamotrigine<br>Levetiracetam<br>Oxcarbazepine<br>Sodium valproate | Carbamazepine<br>Clobazam<br>Lamotrigine<br>Levetiracetam<br>Oxcarbazepine<br>Sodium valproate<br>Topiramate | Eslicarbazepine acetate<br>Lacosamide<br>Perampanel<br>Zonisamide | Gabapentin<br>Phenobarbital<br>Phenytoin<br>Pregabalin<br>Retigabine<br>Tiagabine<br>Vigabatrin |

Table 2. *Recommended place of perampanel in the pharmacological management of partial-onset seizures based on the NICE guidelines*[21] *and the experience of the consensus meeting participants*

*Combining perampanel with other AEDs*

Perampanel is rapidly absorbed after oral administration (Cmax at 0.25–2.0 hours) with an average half-life of 105 hours.[1] The drug is primarily metabolised by cytochrome P450 3A4 (CYP3A4)-mediated oxidation followed by sequential glucuronidation. At clinically-relevant doses, perampanel is neither a potent inhibitor nor an inducer of cytochrome P450 isoenzymes. However, since it is metabolised via CYP3A4, concomitant administration of AEDs that are CYP3A4 inducers (e.g. carbamazepine, oxcarbazepine, phenytoin and topiramate) will increase perampanel clearance and reduce perampanel plasma concentrations.

Pharmacokinetic/pharmacodynamic modelling using data from the phase 3 studies suggests a significant association between increases in perampanel plasma concentrations and reductions in seizure frequency,[22] indicating that patients taking enzyme-inducing AEDs may require higher doses of perampanel to optimise their clinical outcomes. This is supported by the results from the pooled analysis of the phase 3 studies,[9] which reported reduced efficacy when perampanel 12 mg/day was added to carbamazepine (median % change in frequency of all partial seizures –20.3%; 50% responder rate for all partial seizures 31.3%) than when added to sodium valproate (–37.2%; 36.5%, respectively), lamotrigine (–31.2%; 30.6%, respectively) or levetiracetam (–34.7%; 43.0%, respectively). The analysis confirmed, however, that perampanel is effective in all AED combinations assessed.

**Consensus statement 5:** Perampanel may be combined with other AEDs with good efficacy outcomes. A higher dose of perampanel may be required in patients taking enzyme-inducing AEDs.

*Perampanel dosing and titration*

Perampanel should be taken once-daily before bedtime.[1] Treatment should be initiated at a dose of 2 mg/day and titrated in 2 mg/day increments to a maintenance dose of 4–8 mg/day according to individual response.[1] Depending on individual response and tolerability, the dose may be increased to a maximum recommended dose of 12 mg/day.[1]

In clinical trials, perampanel doses were titrated in 1- to 2-weekly intervals, however, 'real-world' data and experience in clinical practice suggests improved tolerability and treatment retention with a slower dose titration schedule. The group confirmed that, in their experience, perampanel doses should be increased every 4 weeks according to clinical need to achieve the MTD (up to a maximum dose of 12 mg/day). If there is no evidence of clinical benefit once the MTD has been reached, treatment withdrawal should be considered.

**Consensus statement 6:** Perampanel should be initiated at a dose of 2 mg/day, taken at bedtime, and titrated by increments of 2 mg every 4 weeks according to clinical need to achieve the maximum tolerated dose (MTD) (up to 12 mg/day). Consider withdrawing perampanel if there is no evidence of clinical benefit once the MTD has been reached.

## Summary and conclusions

Perampanel is a valuable addition to the armamentarium for treating partial-onset seizures and preventing secondary generalisation. Its unique mode of action, ease of use, and good efficacy and tolerability profile make it potentially suitable for use as an adjunctive therapy in most treatment-refractory patients aged 12 years and older with partial epilepsy. Clinicians should consider perampanel as a 2nd-line adjunctive therapy option in patients who have not responded adequately to other AEDs.

Perampanel treatment may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Experience in clinical practice suggests that perampanel should be titrated slowly to the MTD (up to 12 mg/day) to enhance tolerability and treatment retention. Ongoing prescribing of perampanel may be undertaken in primary care with support from a consultant neurologist or epilepsy specialist nurse if required.

## Acknowledgements

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## References

1. *Fycompa® (perampanel) 2mg, 4mg, 6mg, 10mg, 12mg film-coated tablets. Summary of Product Characteristics.* Eisai Ltd. Revision dated 29 September 2014. Available at: http://www.medicines.org.uk/emc/medicine/26951/. Last accessed 7 January 2015.
2. Eisai Ltd. Data on file PER093.
3. Rogawski MA, Hanada T. *Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. Acta Neurol Scand* Suppl 2013;(197):19–24.
4. Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, Ogasawara A, et al. *Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy.* Epilepsia 2011;52(7):1331–40.
5. French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. *Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304.* Neurology 2012;79(6):589–96.
6. French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. *Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305.* Epilepsia 2013;54(1):117–25.
7. Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al. *Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures.* Neurology 2012;78(18):1408–15.
8. Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, Clément JF, et al. *Long-term safety of perampanel and seizure outcomes in refractory partial-onset seizures and secondarily generalized seizures: results from phase III extension study 307.* Epilepsia 2014;55(7):1058–68.
9. Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, et al. *Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies.* Epilepsia 2013;54(8):1481–9.
10. Steinhoff BJ, Hamer H, Trinka E, Schulze-Bonhage A, Bien C, Mayer T, et al. *A multicenter survey of clinical experiences with perampanel in real life in Germany and Austria.* Epilepsy Res 2014;108(5):986–8.
11. Villanueva V, Garcés M, López-Gonzalez FJ, Rodriguez-Osorio X, Rodriguez-Uranga J, López-Gomáriz E, et al. *FYDATA study: retrospective analysis of perampanel in a real-life setting.* Poster presentation at the 88th Annual Meeting of the American Epilepsy Society, Seattle, WA, USA. 5–9 December 2014. Abstract 1.332.
12. Keogh S, Greenhill L, O'Donnell M, McCorry D, Bagary M. *The efficacy and tolerability of perampanel (Fycompa) in everyday clinical practice using a retrospective multicentre audit.* Epilepsia 2014;55(Suppl 2):118 (Abstract p358).
13. Sieradzan KA, Hodgson H. *Efficacy and tolerability of perampanel in patients with refractory partial epilepsy in a tertiary epilepsy centre.* Epilepsia 2014;55(Suppl 2):50 (Abstract p137).
14. Lawthom C, Powell R, Hillman E, John K, Talbert A, Hamandi K. *Perampanel in South Wales: A multi-centre clinical evaluation.* Epilepsia 2014;55(Suppl 2):51 (Abstract p138).
15. Parrett MP, McLean BN, Shankar R, Cox D. *A service evaluation of perampanel in Cornwall, UK.* Epilepsia 2014;55(Suppl 2):110 (Abstract p334).
16. Kelly K, Stephen LJ, Parker P, Brodie MJ. *Adjunctive perampanel in highly drug-resistant localization-related epilepsy – a prospective audit.* Epilepsia 2014;55(Suppl 2):44 (Abstract p119).
17. Goulding PJ, Wright E, Geldard J, Maguire M. *A service evaluation of perampanel (Fycompa) at Leeds General Infirmary.* Epilepsia 2014;55(Suppl 2):111 (Abstract p335).
18. Manidakis I, Cock H, Loszardi D, Moran N, Nashef L, Richardson M, et al. *Perampanel in the treatment of epilepsy: a multicentre evaluation.* Epilepsia 2014;55(Suppl 2):182 (Abstract p562).
19. Coyle H, Clough P, Cooper P, Mohanraj R. *Clinical experience with perampanel: focus on psychiatric adverse effects.* Epilepsy Behav 2014;41:193–6.
20. Flynn C, Delanty N. *Seizure response to perampanel in a severe refractory group of epilepsy patients.* Epilepsia 2014;55(Suppl 2):113 (Abstract p343).
21. National Institute for Health and Clinical Excellence. *The diagnosis and management of the epilepsies in adults and children in primary and secondary care.* Clinical Guideline 137. January 2012.
22. Gidal BE, Ferry J, Majid O, Hussein Z. *Concentration-effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures.* Epilepsia 2013;54(8):1490–7.

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**PRESENTATION:** Film-coated tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg perampanel.

**INDICATION:** Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

**DOSE AND ADMINISTRATION: Adults and Adolescents:** Starting dose is 2 mg daily. Dose should be titrated based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of between 4 mg/day to 12 mg/day. Dose should be taken orally once daily before bedtime. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel should be titrated no more frequently than at 1-week intervals. Withdraw gradually. **Elderly and patients with renal or hepatic impairment:** Dosage adjustments not required in elderly patients. Dosage adjustments not required in mild renal impairment, not recommended in patients with moderate or severe renal impairment or patients undergoing haemodialysis. Caution in mild or moderate hepatic impairment, titration should not be faster than every 2 weeks and maximum daily dosage not exceeding 8 mg. Not recommended in severe hepatic impairment. **Children and adolescents under 12 years:** No data available.

**CONTRA-INDICATIONS:** Hypersensitivity to perampanel or any excipient.

**PREGNANCY:** Not recommended.

**LACTATION:** Unknown if excreted into breast milk. A decision whether to discontinue breastfeeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

**WARNINGS AND PRECAUTIONS:** Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. At doses of 12 mg/day Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives. There appears to be an increased risk of falls, particularly in the elderly. Aggressive and hostile behaviour has been reported; patients and caregivers should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted; the dosage of perampanel should be reduced if such symptoms occur and should be discontinued immediately if symptoms are severe. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse. Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, or switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly. There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with perampanel. Fycompa contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**DRUG INTERACTIONS:** The possibility of decreased efficacy of progestative-containing oral contraceptives should be considered for women needing Fycompa 12 mg/day and an additional reliable method (intra-uterine device (IUD), condom) is to be used. Carbamazepine, phenytoin, oxcarbazepine and topiramate have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel. Fycompa did not affect in a clinically relevant manner the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid. The effect of perampanel on monohydroxycarbazepine concentrations is not known. Fycompa (6 mg once daily for 20 days) decreased midazolam AUC by 13% in healthy subjects. Strong inducers of cytochrome P450 such as rifampicin and hypericum are expected to decrease perampanel concentrations. Felbamate has been shown to decrease the concentrations of some drugs and may also reduce perampanel concentrations. Ketoconazole, a CYP3A4 inhibitor, increased perampanel AUC by 20% and prolonged perampanel half-life by 15%. Strong inhibitors of other cytochrome P450 isoforms could potentially also increase perampanel concentrations. Fycompa used in combination with other central nervous system (CNS) depressants such as alcohol can increase levels of anger, confusion, and depression. The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol.

**SIDE EFFECTS:** Adverse reactions most commonly lead to discontinuation of perampanel were dizziness and somnolence. Refer to SPC for all side effects. *Very common effects (≥1/10)*: dizziness, somnolence. *Common effects (≥1/100, <1/10)*: decreased appetite, increased appetite, aggression, anger, anxiety, confusional state, ataxia, dysathria, balance disorder, irritability, diplopia, vision blurred, vertigo, nausea, back pain, gait disturbance, fatigue, weight increased, falls. Based on the clinical trial database of 143 adolescents, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults.

**LEGAL CATEGORY:** POM

**BASIC UK NHS COST:** Fycompa 2 mg: packs of 7 £35.00, Fycompa 4 mg: packs of 28 £140.00, Fycompa 6 mg: packs of 28 £140.00, Fycompa 8 mg: packs of 28 £140.00, Fycompa 10 mg: packs of 28 £140.00, Fycompa 12 mg: packs of 28 £140.00.

**IRISH PRICE TO WHOLESALER:** Fycompa 2 mg: packs of 7 €40.95, Fycompa 4 mg: packs of 28 €163.80, Fycompa 6 mg: packs of 28 €163.80, Fycompa 8 mg: packs of 28 €163.80, Fycompa 10 mg: packs of 28 €163.80, Fycompa 12 mg: packs of 28 €163.80.

**Marketing authorisation numbers:** Fycompa 2 mg 7 tablets: EU/1/12/776/001, Fycompa 4 mg 28 tablets: EU/1/12/776/003, Fycompa 6 mg 28 tablets: EU/1/12/776/006, Fycompa 8 mg 28 tablets: EU/1/12/776/009, Fycompa 10 mg 28 tablets: EU/1/12/776/012, Fycompa 12 mg 28 tablets: EU/1/12/776/015.

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# Reaching down the rabbit hole:

## A Renowned Neurologist Explains the Mystery and Drama of Brain Disease

Despite the diagnostic brilliance described in this day-in-the-life portrayal of Dr Ropper's professional life, the titular rabbit is not that which is traditionally pulled from a hat. Rather, the title refers to the White Rabbit's entry into Wonderland, where a bewildered Alice is advised by the Red Queen to believe six impossible things before breakfast.

Ropper sees his job as reaching to pull patients from their other-wordly holes of neurological dysfunction. In doing so, he is more than content with the six improbable things that must be confronted each morning. And the improbables are what make this book so memorable, including a gag that may help readers understand its provenance: a grandmother takes an afternoon stroll, pushing the latest addition to the family, when a friend stops to comment on how beautiful the baby is. The grandmother's reply is along the lines of "I know, but you should see the pictures".

In this book, the pictures of Ropper's routine clinical work in a very busy professional life are created with the help of a co-author, thought necessary because "no physician, in the moment, can serve the patient and the story". The venture required someone who was willing to follow Ropper at work to "experience life on the ward with me, even without me". 70% of the dialogue is verbatim, 20% recollected, and 10% extrapolated. Some of the case histories are borrowed from colleagues. Although its aim is not to be an "as-told-to" book, it has in parts the feel of an as-heard-by-a-journalist account. Brian Burrel the coauthor, is described as having a "lyrical talent for making true stories sing, which is perhaps as much a warning as a recommendation.

But the book is very readable. Personal details and straight-talking observations are juxtaposed with clinically-relevant insights into Ropper's approach, the influence of his colleagues (junior and senior, past and present), and the environment in which they work. The tempo is energetic and energising and the clinical wisdom will raise smiles. The Raymond Chandler-like descriptions (he relates the description by one doctor of a patient as a "slob of a tattooed smoker"; another has "nostrils like a racehorse"), the no-nonsense description of colleagues (the "Irish approach") and the casual nature of some of the reported conversations (he admits that when dealing with patients with functional disorders that he has "no spiel to offer, and sometimes revert to being a jerk") will also raise eyebrows. Those eyebrows may be alternately raised and lowered, together and separately, because it is difficult not to identify with the situations being described. The atmosphere is "on edge"; the patients are at the very edge, some an eyelash away from being locked in.

Some of the writing should be compulsory reading in medical curricula. The most powerful is perhaps the description of a patient's death. Undeterred by the consequences of finding evidence of a potentially-treatable condition, with candour and humility, he requests a post mortem examination. Subsequently, he leads the junior staff to the morgue. His arresting on-the-slab description of the epidural abscess, there to be seen and handled by staff who might have managed things differently, is a call to arms for the educational value of post mortems. All the books, the diagrams and web searches will never match the evisceratingly memorable effect of touching reversibly-diseased organs laid out by an interested and understanding pathologist - as our Pathology, so our practice. Post mortems can change the persective of those in attendance; they can change people in to proper doctors. Ropper's metaphor – he cranes his neck to see over the shoulders of his (and our) professional ancestors, to be reminded of their thoughts when they looked at similar clinical and pathological material – is spot on. As a finale, he points out that Medicare does not pay for post mortems – it is not part of their package. The Medicare boxes may be ticked, but it takes clinicians like Ropper to force institutions to think outside them. Bravo.

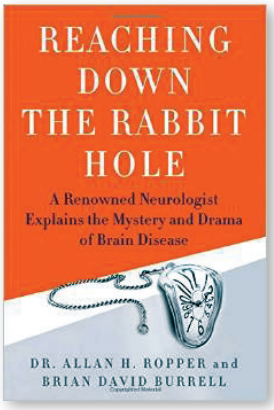
In stark educational contrast is the decision to visit George, a patient not seen since being diagnosed with Motor Neurone Disease more than five years before. George is at home, tetraplegic and ventilated. Ropper describes a conversation wherein he explains to George, and George's wife, his recent role in allowing a patient with motor neurone disease to die. Ropper asks "Are you a little bummed out that I would be part of this?". Thankfully, they assure him that they are in support of people making their own decisions under such circumstances.

The account contains little of Ropper's inner conversation when managing this most testing of conditions but does describe his leaving George's home and driving back across the causeway as dusk approaches – back to his wife, his house, his dog, his ham radio pals, his life, and his new friend Sheldon to whom he later confides that "life is too serious to be taken entirely too seriously". The juxtaposition of the banal with the profound, the casual with the clinical, and the recognisably real with the portrayed image left me thinking of this book as something of a plumber's handkerchief:[1] it is not entirely clear to what uses it will be put.

However, even if the authorial double act has nudged some of the writing away from the scientific, those parts that are more Ropper and Adams than Ropper and Chandler, more clinical looking glass than Wonderland, make for an improbably intriguing read.

Reference

1. Chandler R. *Farewell, My Lovely*, 1940.

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***Reviewed by:***
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> *Hippocratic writings resound on many of its pages: "And men ought to know that from nothing else but from the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations.*

# Postconcussion Syndrome/Disorder or Mild Traumatic Brain Injury: diagnostic issues and treatment

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**Introduction**

Traumatic brain injury at the milder end of the spectrum is far more common than moderate-severe spectrum. Mild traumatic injury (mTBI) accounts for approximately 80% of traumatic brain injuries.[1] Traumatic brain injuries at the milder end of the spectrum which lead to persisting difficulties have been referred to as postconcussion syndrome/postconcussion disorder.[2,3] Individuals with persistent difficulties following a traumatic brain injury at the milder end of the spectrum may be assessed and treated by Neurology, Neuropsychology, and Neuropsychiatry. There has been ongoing research looking at outcome following traumatic brain injury at the milder end of the spectrum, the validity of postconcussion syndrome/disorder, and treatment of symptoms following milder traumatic brain injuries. This paper will review some of the research in these important areas within neurorehabilitation.

**Diagnostic issues**

Postconcussion syndrome/disorder is listed in both the ICD-10 and DSM-IV-TR (ICD, DSM-IV-TR). The diagnostic criteria for postconcussional syndrome in the ICD-10 includes a history of head trauma with loss of consciousness preceding symptom onset by a maximum of four weeks. In addition there needs to be symptoms in three or more of the following symptom categories: Headache, dizziness, malaise, fatigue, noise tolerance; irritability, depression, anxiety, emotional lability; subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment; insomnia; reduced alcohol tolerance; preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of the sick role.[2]

The DSM-IV-TR criteria for postconcussional disorder requires a history of head trauma that has caused significant cerebral concussion. Secondly there is evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention (concentrating, shifting focus of attention, performing simultaneous cognitive tasks), or memory (learning or recalling information). Thirdly, three (or more) of the following occuring shortly after the trauma, and lasting at least three months: becoming fatigued easily; disordered sleep; headache; vertigo or dizziness; irritability or aggression with little or no provocation; anxiety, depression, or affective lability; changes in personality (e.g. social or sexual inappropriateness); apathy or lack of spontaneity. The symptoms must have their onset following head trauma or else represent a substantial worsening of pre-existing symptoms. The disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.[3]

There are clear differences in the two diagnostic systems. Firstly, the ICD refers to a syndrome whereas DSM refers to a disorder. Secondly, the ICD requires that the individual has lost consciousness whereas this is not a criterion in the DSM. The DSM requires evidence from neuropsychological testing or quantified cognitive assessment of difficulty in a cognitive domain/s. This is not included in the ICD-10 classification system.

Over the last ten years there has been research looking at the non-specificity of the symptoms within postconcussional syndrome/disorder. Studies show that post-concussive-like symptoms are generally not related to traumatic brain injury at the milder end of the spectrum, particularly as time goes by, but instead are associated with accompanying acute post-traumatic stress, chronic pain, depression or anxiety disorders.[4,5] Donnell et al's recent study demonstrates this very clearly. They identified participants from 4462 randomly sampled male US Army veterans who served during the Vietnam era. Only 32% of veterans with a history of mTBI met DSM-IV symptom criteria for PCS as compared to 40% of those diagnosed with post-traumatic stress disorder (PTSD), 50% with generalised anxiety disorder (GAD), 57% with major depressive disorder (MDD), and 91% with somatisation disorder.[6] The results were consistent with existing literature showing that the PCS symptoms are not unique to concussion.

The trend within neuropsychology outcome research has been to focus on outcome following mTBI rather than postconcussion syndrome/disorder. mTBI is generally defined as one in which the individual is not unconscious for longer than 30 minutes, post-traumatic amnesia does

not extend beyond 24 hours, and the individual's Glasgow Coma Scale score is 13/15 within 30 minutes of the injury.[7] The outcome research predominantly points to individuals making a full cognitive recovery within days to weeks of the injury.[1] If cognitive difficulties persist the cause is due to other factors such as depression, post-traumatic stress disorder, chronic pain, and psychological factors.[1,3]

The questions regarding the validity of postconcussional disorder are reflected in the latest version of the DSM, the DSM-5. There is no longer a category for postconcussional disorder in the DSM-5. There is a new disorder known as the "Neurocognitive disorders".[8] Within the spectrum of neurocognitive disorders there is a new category "Major or Mild Neurocognitive Disorder due to Traumatic Brain Injury". There is no longer reference to postconcussional disorder but rather to different severities of traumatic brain injury which include mild TBI, moderate TBI, and severe TBI. Neurocognitive symptoms associated with mTBI are noted to resolve within days to weeks after the injury with complete resolution by three months (DSM-5). It is not known whether postconcussional syndrome will be revised in the next version of the ICD.

**Treatment issues**

Treatment is divided into two broad categories: rest, education and reassurance in the days/weeks following the mTBI, and treatment at the stage at which symptoms have become more persistent.

In terms of treatment at the early stages, most guidelines include physical and cognitive rest followed by a graded increase in activities with reduction in activities if symptoms return or are exacerbated.[9] One of the most effective approaches to management of mTBI is patient education. Ponsford et al showed that by just giving an information booklet at one week post injury led to fewer reported symptoms at three months compared to a control group that did not receive the information booklet.[10] These interventions need not be intensive and are most effective when introduced during the acute or subacute recovery phase after mTBI.[1]

Specific treatments for mTBI at the later stages are divided into pharmacotherapy, cognitive rehabilitation, and psychotherapy.[11] In terms of pharmacotherapy, this can include medication for headaches, as well as medication for anxiety and depression. In general selective serotonin reuptake inhibitors are preferred first line agents because of their relatively benign side effect profile and lower cost generic availability.[12] Cognitive rehabilitation involves looking at compensatory strategies to manage specific cognitive difficulties such as memory difficulties.[11]

In terms of psychotherapy there is a growing trend with regards to the use of cognitive behavioural therapy in the treatment of mTBI individuals who have developed persistent symptoms, with some positive results.[13] Recently there has been a pilot study looking at a mindfulness based stress reduction programme with individuals who have suffered a mTBI with persistent symptoms. Clinically meaningful improvements were noted on measures of quality of life after this intervention.[14] McCrea et al stress the importance of taking a biopsychosocial approach to the management of chronic symptoms after mTBI i.e. taking into account pre-injury factors, on-going physical issues, psychological factors, and the social context of the individual.[15] There is a further important point, and that is clinicians need to consider exaggeration of symptoms or functional elements in cases of persistent symptoms where there is the potential for secondary gain.[1]

There is growing interest in identifying oculomotor and vestibular disturbances in individuals with persistent symptoms following mTBI. Ellis et al have recently presented an approach to managing acute concussion and postconcussion disorder by identifying dysfunction within specific neurological subsystems.[16] This includes a physiological based postconcussion disorder (disordered alterations in global cerebral metabolism), vestibulo-ocular postconcussion disorder (persistent postconcussion symptoms caused by dysfunction of the vestibuleocular system) and cervicogenic postconcussion disorder (persistent postconcussion symptoms caused by dysfunction of the cervical spine and somatosensory system). The authors identify a range of treatment options including vestibular therapy, vision therapy, and medication. Large scale studies looking at the efficacy of vision and vestibular therapy are clearly needed.

**Conclusions**

It is important for clinicians to be aware that there is a move away from diagnosing postconcussion disorder. This is most clearly demonstrated in the DSM-5 which no longer includes the diagnostic category of postconcussion disorder. It will be important for clinicians to review the next version of the ICD to see whether the disorder of postconcussion is amended or taken out altogether as has occurred in the DSM-5.

Clinicians need be cautious when using the term postconcussion syndrome/ disorder as it implies all the present symptoms are attributable to the traumatic brain injury. There is now a more nuanced understanding of symptoms following mTBI and that not all symptoms are attributable to the initial brain injury. It may be more helpful to individuals to be provided with an explanation as to the likely causes of their various symptoms which may include depression/ chronic pain/ vestibular difficulties. This of course would be predicated on a comprehensive assessment in order to determine the cause of the various on-going symptoms.

A consensus has yet to emerge regarding the best treatment for treating mTBI. Part of the difficulty in finding one effective treatment for the symptoms following a mTBI is that there are so many possible causes of on-going difficulties. The range of possible causes for on-going problems include pre-injury factors, current psychiatric diagnoses, vestibular issues, chronic pain, malingering, and various combinations of these factors.[1,15] When one considers the complexity in mTBI cases it is therefore not surprising that there is not a clear single treatment which has been shown to be effective in treating persisting symptoms. However, in reviewing the literature it is clear that progress is being made in terms of expanding the number of treatment options for individuals with persistent symptoms following mTBI.[1]

REFERENCES


1. McCrea,M. *Mild traumatic brain injury and post-concussion syndrome. The new evidence base for diagnoses and treatment.* New York: Oxford University Press, 2008.
2. World Health Organisation. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.* Geneva, Version 2007.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM IV-TR).* 4th ed. Washington: 2000.
4. Smith-Seemiller L, Fow NR, Kant R, Franzen MD. *Presence of post-concussion syndrome symptoms in patients with chronic pain vs mild traumatic brain injury.* Brain Injury, 2003;17: 199-206
5. Iverson, G *Misdiagnosis of the persistent postconcussion syndrome in patients with depression.* Archives of Clinical Neuropsychology. 2006:358:453-463.
6. Donnell A, Kim M, Silva M, Vanderploeg. *Incidence of Postconcussion Symptoms In Psychiatric Diagnostic Groups, Mild Traumatic Brain Injury and Comorbid Conditions.* The Clinical Neuropsychologist. 2012;26:1092-1101.
7. Mild Traumatic Brain Injury Committee, A.C.o.R.M, *Head Injury Interdisciplinary Special Interest Group. (1993). Definition of mild traumatic brain injury.* Journal of Head Trauma Rehabilitation, 8(3);86-87.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.* DSM-5. USA: 2013.
9. Willer B, Leddy JJ. *Management of concussion and post-concussion syndrome.* Current Treatment Options in Neurology 2006;8:415-426
10. Ponsford J Willmott C, Rothwell A, Cameron P, Kelly AM, Nelms R, Curran C. *Impact of early intervention on outcome following mild head injury in adults.* J Neurol Neurosurg Psychiatry. 2002 Sep;73:330-2.
11. Comper P Bisschop SM, Carnide N, Tricco A. *A systematic review of treatments for mild traumatic brain injury* Brain Inj . 2005; 19:863-80.
12. Walker W Kunz R. (2011). *Postconcussion Syndrome Symptom Management. In Zollman,S. (Ed) Manual of Traumatic Brain Injury Management.* New York: Devos Medical Publishing.
13. Potter S and Brown R. *Cognitive behavioural therapy and persistent post-concussional symptoms: Integrating conceptual issues and practical aspects in treatment.* Neuropsychological Rehabilitation. 2012. 22: 1-25
14. Azulay J, Smart CM, Mott T, Cicerone KD.*A pilot study examining the effect of mindfulness-based stress reduction on symptoms of chronic mild traumatic brain injury/postconcussive syndrome.* J Head Trauma Rehabil. 2013; 28(4):323-311
15. McCrea, M., Iverson, G.L., McAllister, T.W., Hammeke, T.A., Powell, M.R., Barr, W.B., & Kelly, J. P. *An integrated review of recovery after mild traumatic brain injury (MTBI): implications for clinical management.* Clin Neuropsychol, 2009:23(8),1368-1390.
16. Ellis M; Leddy J; Willer B. *Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: An evidence-based classification system with directions for treatment.* Brain Injury. 2014:14:1-11.

# Extending our understanding of the dopaminergic basis of non-motor symptoms in Parkinson's disease

***Highlights of a symposium held at the 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders, 5th December 2014, Nice, France***

## Key points

- **Parkinson's disease (PD) is not just a motor disorder – it comprises both motor and non-motor symptoms (NMS), both of which require effective management to optimise patient outcomes**
- **NMS are known to occur across all stages of PD and place a significant burden on health-related quality of life (HRQoL)**
- **The clinical assessment of PD patients needs a combined approach comprising assessment of total NMS burden in addition to classical motor symptom scoring**
- **Mild cognitive impairment (MCI-PD) can be diagnosed in up to 15% of de novo PD cases and shows conversion into PD dementia (PDD) in >60% of MCI cases within four years**

Parkinson's disease (PD) is traditionally considered as a motor disorder but there is increasing recognition that it is a mixed disorder comprising both motor and non-motor features. Non-motor symptoms (NMS) are now known to occur across all stages of PD, often before motor symptoms develop (1-3). The wide range NMS experienced by people with PD places a significant burden on their health-related quality of life (HRQoL) (4), however symptoms such as low mood, pain, apathy, fatigue and sleep problems often go undeclared to the clinician and therefore remain undertreated. At the 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders held in Nice, France, in December 2014, an international faculty, chaired by Professor Amos Korczyn (Tel Aviv, Israel), discussed the latest developments in our understanding of the underlying aetiology and clinical burden of non-motor features in PD.

Professor K. Ray Chaudhuri (London, UK) noted that in clinical practice PD presents with considerable phenotypic and pathophysiological heterogeneity and evidence suggests that the total 'burden' of NMS, not just the occurrence of individual NMS such as depression, is the major determinant of HRQoL (4). Data from eight international studies including over 2,500 PD patients indicate that most PD patients will report at least eight different NMS when assessed with the Non-Motor Symptoms Questionnaire, NMSQuest (5)(Table 1). Recognising the significant contribution of NMS to the total clinical picture in PD, he proposed that in order to provide a more comprehensive grading of PD severity, the clinical assessment of PD patients needed a combined approach using both the validated Non-motor Symptoms Scale (NMSS) to assess total NMS burden in addition to classical motor symptom scoring (6). In addition, a recent study in newly-diagnosed PD patients suggests there may be NMS-dominant subtypes of PD which has implications for selection of therapy (7).

**Table 1: Prevalence of non-motor symptoms from published studies assessed using NMSQuest (5).** *Reproduced with permission from Pract Neurol.*

| NON-MOTOR SYMPTOMS | MEAN (%) | RANGE (%) |
|---|---|---|
| **Cognitive** | | |
| Memory | 45.8 | 37.9–62.5 |
| Concentration | 38.7 | 29.6–50.0 |
| **Depression** | | |
| Sadness | 42.5 | 22.5–56.0 |
| Anxiety | 43.4 | 30.7–55.8 |
| **Sleep** | | |
| Excessive daytime somnolence | 30.5 | 21.2–37.5 |
| Insomnia | 40.9 | 17.6–52.5 |
| REM sleep behaviour disorder | 34.2 | 29.6–38.7 |
| Restless legs syndrome | 35.8 | 27.7–41.1 |
| **Fatigue** | 41.5 | 31.1–58.1 |
| **Pain** | 31.1 | 18.2–45.9 |
| **Gastrointestinal** | | |
| Swallowing | 25.4 | 16.1–30.3 |
| Constipation | 46.5 | 27.5–71.7 |
| **Urinary** | | |
| Urgency | 53.4 | 35.0–61.0 |
| Nocturia | 53.8 | 26.4–66.7 |
| **Global comparison** | | |
| NMSQ-PD | 8.3 | 4.0–19.0 |
| NMSQ-C | 3.5 | 2.0–12.0 |

Professor Teus van Laar (Groningen, The Netherlands) highlighted the common problem in PD patients of mild cognitive impairment (MCI-PD) which can be diagnosed in up to 15% of de novo cases and shows conversion into PD dementia (PDD) in >60% of MCI cases within four years (8). Posterior cortical dysfunction has been shown to be a predictor of cognitive decline in PD patients (9) as are clinical markers of cholinergic degeneration, such as olfaction and gait. Receptor imaging studies show cholinergic depletion occurs early in the disease course. Visual hallucinations (VH) are known to be a marker of cognitive decline and cholinergic depletion and are thought to be due to dopaminergic overstimulation which often results in effective PD medication being reduced. However, studies have shown that subcutaneous apomorphine can be used in PD patients with VH, MCI-PD or PDD without causing symptom deterioration (10, 11). Notably, preliminary studies show it may potentially reduce cognitive decline by decreasing beta-amyloid plaques (12).

***References***


1. Chaudhuri KR, et al. Lancet Neurol. 2006;5(3):235-45.
2. Barone P, et al. Mov Disord. 2009;24(11):1641-9.
3. Zis P, et al. J Parkinsons Dis. 2014;4(3):541-7.
4. Martinez-Martin P, et al. Mov Disord. 2011;26(3):399-406.
5. Todorova A, et al. Pract Neurol. 2014;14(5):310-22.
6. Chaudhuri KR, et al. PloS One. 2013;8(2):e57221.
7. Erro R, et al. PloS One. 2013;8(8):e70244.
8. Goldman JG, et al. Mov Disord. 2014;29(5):608-21.
9. Williams-Gray CH, et al. Brain. 2009;132(Pt 11):2958-69.
10. Geerligs L, et al. Clin Neuropharmacol. 2009;32(5):266-8.
11. van Laar T, et al. Parkinsonism Relat Disord. 2010;16(1):71-2.
12. Yarnall AJ, et al. Presented at 17th International Congress of Parkinson's Disease and Movement Disorders, Sydney, Australia, June 2013.Abstract LBA-13.


***Prescribing information can be found on the adjacent page***

**This article was commissioned by Britannia Pharmaceuticals Ltd and was written by Helen Lawn & Associates. The Britannia-sponsored symposium was held on 5th December 2014 during the 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders in Nice, France.**

**APO2-0215-0594 Date of preparation: February 2015**


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## RAPID RELIABLE 'ON' FOR PARKINSON'S DISEASE

**APO-go®** Apomorphine hydrochloride
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Consult Summary of Product Characteristics before prescribing. **Uses** Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication **Dosage and Administration** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and broncospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes.
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APO-go Pre filled syringes: PL 06831/0247
**Legal Category** POM
**Date of last revision:** December 2014
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# OPTIMISE data project to capture the experience of multiple sclerosis patients

Researchers will track the lives of people with multiple sclerosis (MS) in unprecedented detail in a project to improve the evaluation of treatments.

To gain a better understanding of MS and its treatments there is a need for a system to collect comprehensive data that provides an in-depth picture of the experiences of MS patients across a large population.

Over an initial three year period, the OPTIMISE project will develop and deploy tools for collecting a wide range of data from people with MS in addition to routine clinical assessments. The project will work to integrate brain scans, genomics data, biomarkers from blood samples, self-reported quality of life measures and data from sensors that track movement into a single database. The project will initially pilot the tools through MS centres in Imperial and three other UK institutions before expanding access to the approach for researchers worldwide.

OPTIMISE is a Joint Working collaboration between Imperial College London and the biopharmaceutical company Biogen Idec. By comprehensively capturing and managing data in ways that can be implemented at a low cost and a large scale, the project will allow researchers to better monitor outcomes and evaluate new treatments. This will also help to develop more personalised therapeutic approaches based on an understanding of the individual factors that contribute to the progression of MS.

Transparency of data and open access are at the heart of the project. OPTIMISE will collect both clinical and patient-centred data with the longer-term aim of making these data accessible to both researchers and the patients who contributed. Biogen Idec has provided initial funding for development of the OPTIMISE IT software and the collaboration also intends to facilitate links with MS registries across Europe, who are already collaborating with Biogen Idec. The collaboration will bring additional "in kind" resources for analyses of data in ways that will contribute to patient benefit.

Professor Paul Matthews, Principal Investigator on the OPTIMISE project and Edmond and Lily Safra Chair in Translational Neuroscience and Therapeutics at Imperial College London, said, "This important collaborative project is underpinned by support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre. It will enable a new level of clinical research for MS. It will aggregate data from MS patients and their carers to provide a detailed picture of how the disease affects them and how well current treatments work. Although led by Imperial, this initiative has grown out of a co-operative vision developed between most of the major MS centres across the UK. Looking forward, we intend that this public-private collaboration will grow with the same spirit of cooperation."

Dr Fiona Thomas, UK and Ireland Director of Medical Affairs, Biogen Idec, added, "This innovative project heralds the first systematic and multi-centre collection of patient, physician and MRI data in the UK to better inform doctors, the health service and industry about patient needs. This will facilitate critical analysis of MS patient populations allowing clinicians to offer more personalised management of their disease."

The OPTIMISE portal will use a custom-made software platform developed at the Big Data Institute at Imperial College London to store, curate and analyse data. A central element of the project will be an open access website (www.optimise-ms.org)to allow researchers to share, manage and analyse data within a secure framework.

Patients can use the system to report outcomes and also to discuss the project with other participants and provide feedback to the researchers. Smartphone apps will capture GPS data from movement sensors to monitor patient mobility. OPTIMISE is currently in the planning stages.

For further information on the project please contact Sally Rennick on s.rennick@imperial.ac.uk

# European research initiative for the prevention of Alzheimer's dementia

The members of the EPAD initiative recently announced the start of a novel collaboration between academic and private sectors to test innovative treatments for the prevention of Alzheimer's dementia.

Previous attempts to bring new drugs for Alzheimer's disease to the market have been disappointing despite a high level of investment. However, the realisation that Alzheimer's disease is a progressive disorder and that early intervention may be more effective has led to research efforts being focused on prevention.

The goal of the initiative is the prevention of dementia in people with evidence of the disease (such as biomarker abnormalities as identified by specific tests), who still may have little or no complaints or clinical symptoms.

"EPAD is part of a global initiative that will make a fundamental difference to the understanding and management of Alzheimer's disease in people with very early or no symptoms at all. This could be a game-changer. It is only possible because of the absolute commitment of academics, industry, policy makers and the public to work hand in hand to defeat this global threat", said Prof Craig Ritchie, EPAD Co-coordinator and Professor of the Psychiatry of Ageing at the University of Edinburgh.

New tools and methods now allow the identification of patients in the early stages of Alzheimer's disease. This creates an opportunity to have new treatment options investigated in clinical studies early on. A difficulty however remains with the large number of patients and study sites needed to confirm a therapeutic effect within a limited span of time. In contrast to several pharmaceutical companies and academic institutions pursuing this in isolation, a joint effort clearly has advantages: the identification and referral of the concerned patients is accelerated and several treatment options can be tested rapidly within one same trial.

Therefore, EPAD aims to develop a platform using existing information from national or regional patient cohorts or register studies, which have already identified potential patients. Through EPAD, the undertaking of better, adaptive, multi-arm proof of concept studies for early and accurate decisions on the ongoing development of drug candidates or drug combinations is facilitated.

All data collected from the cohort and trial will become publicly available for analysis to improve disease models in the pre-dementia phase of Alzheimer's disease.

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# Association of British Neurologists Annual Meeting 2015 – Harrogate 20-22nd May

In the 17th and 18th centuries Harrogate was famous as a spa town providing visitors with waters and relaxation to boost their health. In the 21st century, well 2015 in particular, it provides the setting to allow you to reinvigorate your neurological knowledge and enjoy neurological camaraderie at the ABN Annual Meeting.

It always seems invidious to pick out highlights for these meetings when we have such a varied and interesting programme – even more so as often some of the most memorable moments come from the scientific papers or from the always thought provoking and informative case competition which are still in the process of being submitted.

This year the teaching and science sessions are not focused on specific disorders or symptoms but interlinked themes. We have a session on channelopathies which involve every level of the nervous system, with talks from Dimitri Kullmann, Belinda Lennox and Nicholas Davies, a 'Clinician's guide to emerging diagnostic investigations' with talks on biomarkers, genetics and imaging from Jonathan Rohrer, Simon Hammans and James Rowe. Neurology overlaps with other specialties, particularly Neurosurgery and Psychiatry, and we are running a session on 'Neurosurgery for Neurologists' with talks on tumours, cervical surgery and normal pressure hydrocephalus by Caroline Hayhurst, William Taylor and Richard Edwards. 'The psychiatric borderlands of neurology' considers the acutely agitated patient, the autistic spectrum and psychosis with talks from Killian Welch, Jeremy Parr and Eileen Joyce. We are running the popular update session again, dealing with MS, CIDP and vasculitis and myasthenia this time round. We are introducing a new session on 'How I would approach a patient with…' where we will hear from Nick Fox on '…cognitive impairment below age 60' and Rob Hadden on '…generalised sensorimotor neuropathy'.

Last year we had case based sessions run by special interest groups. The feedback for these was positive so we have expanded the sessions dedicated to these groups, to allow attendees to sample more. One cannot but highlight our Plenary speakers whose talks are eagerly anticipated. We are delighted that the Gordon Holmes Lecture is being given by Tony Lang who has contributed so much to the scientific and clinical study of movement disorders. Jeremy Farrar, neurologist and the Director of the Wellcome Trust, has recently returned from Vietnam and will telling us about 'World Health and the Neurologist'. The movement disorder theme will be picked up again by the 2015 ABN Medallist, Andrew Lees. Phil Smith is taking over as President – I very much look forward to his Presidential Address.

On the day before the meeting we are running an 'Introduction to Neurology' session for Foundation doctors who are interested in Neurology – are there any Foundation doctors who might be interested? If so please contact the office. The ABNT are running the traditionally very successful Trainee Meeting while Huw Morris has organised an interesting Research meeting on Tuesday evening that draws heavily on personal experience to highlight research advice. Alastair Compston will be talking about Translational neurology in action – CAMPATH, David Burn will be discussing how to run a multicentre study and Jon Rohrer will be telling us what he learnt from his PhD. Members who get to Harrogate on Tuesday evening are welcome to come to this session. In addition, there is a 'Need to Know Neurology' Session for GPs too. So, the Harrogate meeting provides much to look forward to – even if you disregard the dinner and after dinner entertainment (which I hope you won't) – and the opportunities to catch up with friends and colleagues. I look forward to seeing you there.

***Geraint Fuller, President,***
***Association of British Neurologists.***
***Correspondence to E: info@theabn.org,***
***T: 020 7405 4060.***

| | **Wednesday 20 May** | |
|---|---|---|
| 0800 | **ABNT Forum** | **ABN sub committee meetings** |
| 0900 | **Opening and Welcome: President, President Elect** | |
| 0915 | **Teaching/Science session 1 –** Topic: **Neurosurgery for neurologists**<br>Speaker(s): 1. **Richard Edwards, Bristol** Normal pressure hydrocephalus<br>2. **Caroline Hayhurst, Cardiff** Tumour management<br>3. **William Taylor, Glasgow** When I would operate on my own neck | |
| 1045 | **Coffee & Exhibition** | |
| 1115 | **Parallel session 1:** Topic: Audit /quality assurance | **Parallel session 2:** Topic: Clinical Phenomenology |
| 1230 | **Lunch & Exhibition** | |
| | **Novartis Sponsored Symposium**<br>**3 years on: The real world experience with Gilenya, a disease modifying therapy for Multiple Sclerosis** | **Medtronic Sponsored Symposium**<br>**Advanced therapies at an earlier stage: The window of opportunity in Parkinson's disease** |
| 1400 | **Gordon Holmes Lecture** supported by the Guarantors of Brain – Speaker: **Anthony E Lang, Toronto, Canada** | |
| 1445 | **Teaching/Science session 2**<br>Topic: **A clinician's guide to emerging diagnostic investigations**<br>Speaker(s):<br>1. **Jonathan Rohrer, London** Presymptomatic biomarkers in neurodegenerative disease<br>2. **Simon Hammans, Southampton** A genetic cause? What test should I request?<br>3. **James Rowe, Cambridge** Imaging in neurodegeneration: Here, now & in the future | |
| 1615 | **Coffee and Exhibition** | |
| 1645 | **Jeremy Farrar, Director of the Wellcome Trust:** World health and the neurologist | |
| 1745 | **Parallel session 3:**<br>Topic: **Commissioning Neurology Services**<br>Chair: **Ralph Gregory**, ABN, Chair Services & Standards Committee<br>Speakers:<br>1. **David Bateman,** NCD Adult Neurology Conditions<br>2. **James Seward,** PHE: The Neurology Intelligence Network. What can it do for you?<br>3. **Zam Cader,** SCN Lead Thames Valley: Headache: Developing new models of care<br>4. **Chris Kipps**, SCN Lead Wessex: A year in the life of Wessex SCN | **Parallel session 4:**<br>Topic: Disease Pathophysiology |
| 1900 | **Drinks reception – ABNT Dinner** | |

| | Thursday 21 May | | | |
|---|---|---|---|---|
| 0715 | **SIG 1: Neuro-ophthalmology**<br>Chair: Gordon Plant<br>**Case-based discussion** | **SIG 2: Myology**<br>Chair: Mike Hanna<br>**Case-based discussion** | **SIG 3: British Neuro-Toxin Network**<br>Chair: Marie-Helen Marion<br>**Case-based discussion** | **SIG 4: Neuro Rehabilitation**<br>Chair: Richard Greenwood<br>**Case-based discussion** |
| 0830 | **Teaching/Science session 3**<br>Topic: **Channelopathies: An open and shut case?**<br>Speaker(s):<br>1. **Dimitri Kullman, London** Ion channels for the neurologist<br>2. **Belinda Lennox, Oxford** Psychiatric channelopathies<br>3. **Nicholas Davies, Birmingham** Neuromuscular channelopathies | | | |
| 1000 | **Coffee & Exhibition** | | | |
| 1030 | **Parallel session 5:** Scientific: Platform presentation<br>Topic: Diagnostics | | **Parallel session 6:** Scientific: Platform presentation<br>Topic: Therapeutics | |
| 1200 | **Lunch & Exhibition** | | | |
| | **Eisai Sponsored Symposium**<br>**A new insight into diagnosis and management of generalised epilepsy** | | **Biogen Idec Sponsored Symposium**<br>**Debate 'Should all MS patients be treated in MS specialist care centres'** | |
| 1330 | **Poster session with discussants** | | | |
| 1430 | **ABN Medallist Lecture**<br>Speaker: **Andrew Lees, London**<br>Citation: **William Gibb** | | | |
| 1515 | **Coffee and Exhibition** | | | |
| 1545 | **AGM** | | | |
| 1700 | **SIG 6: Epilepsy**<br>Chair: Khalid Hamandi<br>**Video session** | **SIG 7: Peripheral Nerve**<br>Chair: Robert Hadden<br>**Case-based discussion** | **SIG 8: Cognition**<br>Chair: Chris Butler / Boyd Ghosh<br>**Case-based discussion** | **SIG 9: Neurological Infection**<br>Chair: Tom Solomon<br>**Case-based discussion** |
| 1800 | | | | |
| 1900 | **Gala Dinner – Majestic Hotel** | | | |

| | Friday 22 May | | | | |
|---|---|---|---|---|---|
| 0730 | **SIG 10: Movement Disorders**<br>Chair: Paul Worth<br>**Case-based discussion** | **SIG 11: Myasthenia Gravis**<br>Chair: Marguerite Hill<br>**Case-based discussion** | **SIG 12: Autonomic**<br>Chair: Gordon Ingle<br>**Case-based discussion** | **SIG 13: TBI**<br>Chair: Colette Griffin<br>**Case-based discussion** | **SIG 14: Neurocritical Care**<br>Chair: Maxwell Damian<br>**Case-based discussion** |
| 0900 | **Case presentation competition** | | | | |
| 1010 | **ABN President's Lecture**<br>Speaker: **Phil Smith** | | | | |
| 1055 | **Coffee and Exhibition** | | | | |
| 1125 | **Teaching/Science session 4**<br>Topic**: The psychiatric borderlands of neurology**<br>Speaker(s):<br>1. **Killian Welch, Edinburgh** The acutely agitated patient<br>2. **Jeremy Parr, Newcastle** Autism spectrum disorder for the neurologist<br>3. **Eileen Joyce, London** Psychosis: what to know | | | | |
| 1250 | **Lunch and Exhibition** | | | | |
| | **6 top posters** | | **Genzyme Sponsored Symposium**<br>**This house believes that the risk of MS outweighs the risk of treatment** | | |
| 1415 | **How I would approach the patient with....**<br>Speakers:<br>1. **Nicholas Fox, London** Cognitive impairment below age 60<br>2. **Robert Hadden, London** Generalised sensorimotor neuropathy | | | | |
| 1500 | **Teaching/Science session 5**<br>Topic: **Which drugs and in what order?**<br>Speaker(s):<br>1. **Neil Scolding, Bristol** MS disease modifying treatments<br>2. **Michael Lunn, London** Vasculitis / CIDP<br>3. **Jon Sussman, Manchester** Myasthenia Gravis | | | | |
| 1630 | **Prize Presentations and Close** | | | | |

# Preview of the Harrogate Meeting – Trainees Edition

***Helen Devine***
is a Neurology ST4 in KSS deanery and completing a PhD at the MRC Centre for Neuromuscular Diseases, NHNN. She is Chair of the ABNT Committee.

***Sayan Datta, BMedSci BMBS***
is a ST5 Neurology Registrar in Yorkshire and is the ABNT Regional Representative; he has worked at Bradford Royal Infirmary and currently Leeds Teaching Hospitals.

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E: h.devine@ucl.ac.uk

***To cite:***
Devine H, Datta S. ACNR 2014;15(1):34.

**Useful links:**

www.yorkshire.com
Yorkshire Tourism homepage

www.bettys.co.uk
Bettys Café Tea Rooms

www.blacksheepbrewery.com
Black Sheep Brewery

www.boltonabbey.com
Bolton Abbey

www.devonshirearms.co.uk
Devonshire Arms Hotel & Spa and Burlington Restaurant

www.fountainsabbey.org.uk
Fountains Abbey & Gardens

www.hicyorkshire.co.uk
Harrogate International Centre

www.rhs.org.uk/gardens/harlow-carr
RHS Harlow Carr Gardens

www.ripleycastle.co.uk
Ripley Castle

www.ruddingpark.co.uk/golf
Rudding Park Hotel, Golf facilities

www.skiptoncastle.co.uk
Skipton Castle

www.theakstons.co.uk
Theakston Brewery

www.theboxtree.co.uk
The Box Tree Restaurant, Ilkley

www.turkishbathsharrogate.co.uk
Harrogate Turkish Baths

www.yorke-arms.co.uk
The Yorke Arms Restaurant, Ramsgill

**The meeting**

The 2015 ABN Trainee session in Harrogate promises to be more stimulating than a stride across the Yorkshire Dales and more refreshing than a cuppa in Betty's tea rooms…

At the neurology road-show, junior doctors and medical students will hear ABN president Geraint Fuller discuss the working life of a neurologist, followed by thought-provoking case-based discussions with Joe Anderson and insights into starting a career in neurology from the ABNT committee.

For neurology trainees, the day will follow the successful format of previous years based around two small-group sessions: this year's cases will be muscle disease and dizziness. A lecture from Gill Sare will enlighten us on stepping up to a consultant role. The finale will be a joint session by experienced consultants discussing their favourite clinical signs and tips from the top!

Back by popular demand, the evening research session will be open to medical students, junior doctors and trainees. This year the focus is on how to get ahead in research with lectures from Alastair Compston on translational neurology, an insight into running a multi-centre study from David Burn and the experience of completing a PhD and where that leads from Jon Rohrer. This will be followed by an informal social evening.

The ABNT dinner will take place on Wednesday 20th May at Brio, a little Italian restaurant with a great reputation located in the centre of Harrogate, only a short stroll from the conference centre. We are also looking forward to a cracking Gala dinner on Thursday evening at the Majestic Hotel.

Finally, there will be an ABNT meeting for all trainees at 8am on Wednesday morning and we would love to see you there, hear your views and listen to what issues you would like the committee to take forward over the next year. For further updates please follow @ABNTrainees on twitter. It promises to be an excellent meeting and we hope to see you there!

To make the most of your trip to Harrogate, Sayan Datta, the ABNT rep in Yorkshire provides an insider's guide to discovering the treasures of Harrogate…

**Welcome to Yorkshire!**

Yorkshire's reputation has soared in recent years: record crowds watched the Tour de France for 'Le Grand Départ', Lonely Planet confirmed that it's the 3rd best place to visit in the world (!) and Yorkshire's medals haul at the 2012 Olympics would have ranked it 12th in the world – if it were a country!

Convinced Yorkshire is 'God's own county'? Then Harrogate is one of its crowning jewels; the historic Spa City sits proudly in North Yorkshire, consistently voted the best (and the happiest) place to live in the UK.

The history extends to the venue itself; the Harrogate International Centre boasts the 1000-seat Edwardian Royal Hall Theatre, re-opened by Prince Charles in 2008, now complemented by modern conference and event space.

**Harrogate itself**

No visit would be complete without stopping at Betty's Café Tea Rooms. Forget the Ritz: the quintessential English (and Swiss…) afternoon tea experience is found here, as well as proper breakfast or lunch options. Harrogate is spoilt for choice as nearby RHS Garden Harlow Carr – well worth a visit in itself – has its own Betty's overlooking the grounds.

There are few places in the UK that host Victorian Turkish Baths; Harrogate's Royal Baths were refurbished in the early 2000s and have been altered little from the original rooms and waters used to wash away the citizens' rheumatism and gout. Nowadays, a more contemporary spa experience is on offer.

If there's time, the best of Harrogate golf is at Rudding Park – visitors are welcome, from the confident amateur to those just wanting to fine-tune their game.

**Surrounding area**

It's hard to fit it all in! Pick from nearby World Heritage Site Fountains Abbey & Studley Royal gardens, or Bolton Abbey on the banks of the River Wharfe; both ruined monasteries as a result of Henry VIII's reformation, now spectacularly beautiful and tranquil tourist spots. Or look to Ripon Cathedral: fourteen centuries of history, featuring medieval woodcarving believed to have inspired Alice in Wonderland author Lewis Carroll.

Castles are aplenty: Ripley, Knaresborough, Skipton and Spofforth. Or just get walking: Fewston Reservoir, Brimham Rocks, Nidd Gorge, Ilkley Moors… there's a lifetime of routes in the Yorkshire Dales.

Fine dining at two of Yorkshire's Michelin starred restaurants are a trip away: the Box Tree in Ilkley and the Yorke Arms in Ramsgill. Or try the award winning Devonshire Arms' Burlington restaurant, and combine with a walk around Bolton Abbey. For ale-lovers, Masham is the home of the Black Sheep and Theakston breweries: both offer tours and food.

We hope you enjoy the meeting and your stay. The 'Welcome to Yorkshire' tourist webpage: www.yorkshire.com is a fantastic source of information for Harrogate and beyond, but also, email me and I'll help if I can mok_sayan@yahoo.com.

*To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th April, 2015*

## March

**National Pain Study Day**
25 March, 2015 (ID 413); London, UK
http://www.royalmarsden.nhs.uk/painmanagement
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

**NEUROLOGY 2015: leading edge neurology for the practising clinician'**
25th March 2015 (half day);
26th March 2015 and
Friday 27th March 2015; London, UK
T. 020 344 84460
E. jean.reynolds@ucl.ac.uk
www.ion.ucl.ac.uk

**Spring School – Inflammation: its role in degeneration and regeneration**
30 March – 1 April, Cambridge, UK
www.brc.cam.ac.uk

## April

**Autism over the Lifespan**
23 April, 2015; Exeter, UK
www.rsm.ac.uk
www.videos.rsm.ac.uk

**CNS Series: Treating Dementia**
30 April, 2015; London, UK
www.rsm.ac.uk
www.videos.rsm.ac.uk

## May

**Recent Studies and the diagnosis of MND**
6 May, 2015; Liverpool, UK
www.rsm.ac.uk
www.videos.rsm.ac.uk

**5th Essential Stroke Imaging Course 9 May, 2015; Liverpool, UK**
Contact: Sam Pickup
T. 0151 7099125
E. essentialcourses@hotmail.com
www.BrainSpineImaging.com

**Psychiatry and society: Will neuro-science change understandings and practices?**
12 May, 2015; London, UK
www.rsm.ac.uk
www.videos.rsm.ac.uk

**Pain Therapeutics**
18-19 May 2015; London, UK
www.smi-online.co.uk/pharmaceuticals/uk/pain-therapeutics

**ABN Annual Meeting**
19-22 May, 2015; Harrogate, UK
E. info@theabn.org

**11th European Paediatric Neurology Society Congress 2015**
27-30 May, 2015; Vienna, Austria
www.epns2015.org

## June

**Registrar PD Masterclass**
16/17th September, 2015; Sheffield, UK
www.parkinsonsacademy.co.uk
for further details.

**Consultant PD Masterclass**
Sheffield, UK
Module 1 - 2, 3rd & 4th June 2015
Module 2 - 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk for further details.

**1st Congress of the European Academy of Neurology**
20-23 June, 2015; Berlin, Germany
E. headoffice@eaneurology.org

**Psychological and Neuropsychological Impact of Paediatric and TYA Cancer on Patients and their Families**
29 June, 2015; London, UK
http://www.royalmarsden.nhs.uk/psychologicalimpact
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

## September

**Paediatric Oncology Solid Tumours Study Day**
14 September, 2015; London, UK
http://www.royalmarsden.nhs.uk/paedsolidtumours
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

## November

**Consultant PD Masterclass – Sheffield**
Module 1 - 2, 3rd & 4th June 2015
Module 2 - 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk
for further details.



## Association of British Neurologists

**Annual Meeting**
**Harrogate 19-22 May 2015**

### 19 May, Pre Meeting Training and Development day

**Foundation year doctors**
- What neurologists do and why
- Case based discussions
- How to get into neurology
- Becoming a neurology trainee
- Clinical skills laboratory

**GP 'Need to Know Neurology'**
- Tremor and Parkinson's disease
- Dizziness – how to sort it out
- Blackouts and epilepsy
- A stroke or not a stroke (or TIA)?
- Hints on headaches
- Making sense of numbness and tingling

**Neurology trainee session**
- Small group teaching: Muscle
- Moving towards consultancy
- Small group teaching: Dizziness in the general neurology clinic
- Clinical skills laboratory

**How to get ahead in Research**
- Translational neurology in action - CAMPATH
- Running a multi centre study
- Lessons I've learned from my PhD and beyond

### 20-22 May ABN Annual Meeting

**Scientific sessions**
- Emerging investigations
- Channelopathies
- Neurosurgery for neurologists
- The psychiatric borderlands of neurology
- Which drugs and in what order?

**Parallel sessions**
- Audit /quality assurance
- Commissioning Neurology Services
- Clinical Phenomenology
- Diagnostics
- Therapeutics
- Disease Pathophysiology

**Special Interest Group sessions**
- Neuro-ophthalmology
- Myology
- British Neuro-Toxin Network
- Neuro Rehabilitation
- Epilepsy
- Peripheral Nerve
- Cognition
- Neurological Infection
- Movement Disorders
- Myasthenia Gravis
- Autonomic
- Traumatic Brain Injury
- Neurocritical Care

**Plenary speakers**
- Anthony E Lang, Toronto, Canada
- Jeremy Farrar, Wellcome Trust

### Future Meetings

**ABN Autumn Meeting 2015**
10 September 2015
Institute of Education, London

**ABN Annual Meeting 2016**
17-19 May 2016
The Brighton Centre, Brighton

**For more information visit www.abn.org.uk**

# The United Kingdom Acquired Brain Injury Forum (UKABIF) 6th Annual Conference

***Conference details:*** 27 November 2014, London, UK.

Over 250 delegates attended the United Kingdom Acquired Brain Injury Forum (UKABIF) 6th Annual Conference, which took place late November last year, at the London headquarters of the Royal College of General Practitioners. The morning presentations focused on commissioning rehabilitation services and were followed in the afternoon by discussions about the issues facing people with a brain injury from both service users and family perspectives.

The diverse audience included members of the interdisciplinary rehabilitation team, case managers, personal injury lawyers, social care workers, voluntary organisations, care providers and people who have had a brain injury.

Dr John Etherington, National Clinical Director for Rehabilitation and Recovery in the Community, NHS England opened the conference by saying that the National Health Service does not focus on rehabilitation, or even consider it to be an important part of healthcare services. However, rehabilitation is everyone's business and all health professionals need to understand that it is important – but that remains a challenge. The vision is that in 10 years, rehabilitation will be a key part of every episode of care from acute all the way through to community services. However, the current commissioning structure is an obstacle to care – for example three months is not long enough for a rehabilitation programme, so why use that disease model to commission services? Dr Etherington emphasised that the right clinical and technical training is required to deliver rehabilitation services and that intensity and a significant duration of rehabilitation treatment is essential to produce outcomes for patients.

Dr Michael Dixon addressed delegates wearing several 'hats', including Chair of the NHS Alliance and the first President and Senior Adviser to the new organisation 'NHS Clinical Commissioners', which was created to represent Clinical Commissioning Groups (CCGs) bringing together the commissioning arms of the NHS Alliance, NHS Confederation and the National Association of Primary Care. He acknowledged that the rehabilitation of people with brain injuries has been haphazard. Dr Dixon acknowledged that rehabilitation commissioning needs to be sorted and in a timely fashion. However, Dr Dixon discussed some of the problems facing CCGs such as the increased cost of health services versus real income and a shrinking budget for patients. The reality, said Dr Dixon, is that 'not everyone's ambitions can be fulfilled'.

An excellent model for commissioning Acquired Brain Injury services was discussed by Neil Brownlee, Head of Service/Long-term Conditions Lead, Northumberland Head Injuries Service at the Northumberland, Tyne and Wear NHS Foundation Trust. This 'one-stop shop' is an integrated health and social care community service for people living in Northumberland who have had a traumatic brain injury. The service provides a holistic, interdisciplinary approach and clients are seen by specialist health and social care professionals. It is a timely and efficient model and has been demonstrating excellent outcomes since it was established 22 years ago. The persons' needs are assessed and goals agreed to maximise the person's independence and involvement in the community. At any one time the service has between 100 and 150 service users with mild, moderate and severe traumatic brain injury.

Over 250 delegates attended the 6th UKABIF Annual Conference which took place at the headquarters of the Royal College of General Practitioners in London's Euston Square in November.

Professor Michael Barnes, UKABIF Chair welcomes delegates.


Neil Brownlee, Head of Service/Long-term Conditions Lead, Northumberland Head Injuries Service at the Northumberland, Tyne and Wear NHS Foundation Trust discussed their excellent model for commissioning Acquired Brain Injury services.


Dr John Etherington, National Clinical Director for Rehabilitation and Recovering in the Community, NHS England said: "By investing [in rehabilitation] we will save money".

Emma Gaudern, EMG Solicitors gave an interesting presentation on the issues and implications of the Mental Capacity Act. Emma currently acts as deputy for around 50 people and represents clients with a range of disabilities and many have significant communication problems. The Revd Dr Joanna Collicutt, Karl Jaspers Lecturer in Psychology and Spirituality, Ripon College, Oxford was thought provoking in her presentation on some of the ethical dilemmas posed by Acquired Brain Injury. Multiple impairments may be involved and they may relate to identity. What makes us who we are? How do we work out who we are? The person's place in society may change after an Acquired Brain Injury or it can impact on memory which can be deconstructed or wiped out for large periods of time. The possibility for conflict is enormous and occurs with the past, present and future self as well as with the family, clinical team and carers.

James Piercy, science communicator and Maureen Le Marinel, past President of UNISON and current National Executive Council Member, both talked about the impact of brain injury on family members. James's life changed dramatically in January 2011 when a serious road accident left him with a severe head injury. He was in hospital for nearly two months and whilst making a remarkable recovery, he still lives with the effects of his injury. James vividly described his recovery process in the context of him having to return to work and provide for his family. Maureen gave a moving talk about her niece, Katie who, at 12 years of age, was involved in a 'hit and run' accident which left her with a brain injury. Maureen outlined the need to involve the family in the rehabilitation programme and also highlighted the need for information. UNISON is currently distributing leaflets to promote the 'Head and Brain Injury Information Signpost', a UNISON and UKABIF joint collaboration. This web-based resource is for people with an Acquired Brain Injury, their families and all professionals involved in their care and support.

For further information, please contact:
Chloë Hayward, UKABIF
T: 0845 6080788 • M: 07903 887655
E: info@ukabif.org.uk • www.ukabif.org.uk

# 25th International Symposium on ALS/MND report

***Course details:*** 5-7 December 2014, Brussels, Belgium. ***Report by:*** Dr Samantha Price, Research Information Co-ordinator, MND Association, UK

Over 800 researchers, clinicians and healthcare professionals attended the MND Association's 25th International symposium on ALS/MND held in Brussels, Belgium from 5 -7 December 2014. With nearly 100 presentations and over 300 poster presentations, the event was filled to the brim with the latest MND science and care practice news.

**AAC technology**

Around 80-95% of people living with MND will face communication problems as their speech deteriorates.

Anna Reeves, The ACE Centre, UK explained in her opening talk that twenty years ago there were just five types of communication aids. Today, there are over 200. Anna said: "All these AAC devices are a bit like a sweet shop saying – look at all these things that can change your life! However, the equipment alone is not the solution, it's using the right device that's best for you that is."

In England, getting access to the right equipment at the right time can be challenging – hence the creation of the AAC referral service. Anna identified and engaged with key politicians with a personal interest in communication, including the Prime Minister, David Cameron: "Engaging with politicians was key for us moving forward. But, there's still a way to go – we've got the funding but now we need to implement it, getting all our services working together. Over time we will evaluate the AAC referral service to ensure equity across the country, so that everyone living with MND gets the AAC tech they need!"

Another key presentation was from Dr Phillipa Rewaj (University of Edinburgh). She explained that people unwilling to accept a non-individualised voice was the main reason for AAC abandonment, and the voice banking project aims to address this.

The bank has 740 donor voices, which can be 'mixed' to create an individualised voice. This means that the researchers can build a voice after just a short 15 minute recording session using what is known as the 'voice cloning tool kit!'

Dr Rewaj said: "We have used voice banking on 55 people living with MND in Scotland, and have already received feedback from 15 of these. We have received some extremely positive feedback and all said that they preferred their individual voice to already existing AAC programmed voices."

**End of life discussions**

The symposium included a debate on the topic of 'End of Life'. Dr Van Den Berg, from the Netherlands, discussed that the legal status of euthanasia may affect how physicians think about it. After issuing a survey to physicians involved in the end of life care of people living with MND, there was an 84% response rate from Dutch physicians compared with 64% in England. This shows that there is more of a discussion in Holland where euthanasia has been legal since 2002.


Anna Reeves

Phillipa Rewaj

Chris McDermott

Martin Turner

Dr Finlay discussed the situation in the UK, where euthanasia is illegal. 77% of GPs opposed changing the law as did 80% of neurologists and 90% of palliative care doctors. Perhaps the more death is a part of your day to day the more this affects your moral disposition on the ending of life. Or the ethics of the physicians going into palliative care may initially be geared against it?

How can we be sure that someone has the capacity to make a valid decision given that 30% of people living with MND have mild cognitive impairment? Presence of depression may also hamper our decision as to whether a patient can make a decision relating to their death. During the discussion, Dr Finlay explained that capacity is not one thing. A person may have the ability to choose a single decision e.g. which treatment they want but they may not have the cognitive resources to make a more complex decision such as a decision to end life.

There may also be a fluctuating desire to die as patients' mood, desires, family relationships change. To illustrate this Dr Finlay tells us to ask people who wish to die, 'what is so terrible about today?' and 'what can I do to improve your day?'

Dr Borasio's talk was fascinating with respect to what effect offering choice to patients has upon their decisions to go through their end of life treatment. Only physician assisted suicide is allowed in Switzerland. Of the people that decided to receive lethal medication, two thirds did not take it. Instead it was kept at home as a safety net if things get worse. It's as if the availability of lethal medication is a preventative to suicide and giving people this control affects their disposition towards ending their own life.

**The Sheffield Support Snood**

Current neck supports available are often restricted. This is because they are designed for other purposes (e.g. such as immobilising the necks of individuals after trauma). This means that people living with MND who experience neck weakness are left with the wrong tool for the job.

Dr Chris McDermott from the Sheffield Institute for Translational Neuroscience (SITraN) said: "People living with MND asked us – can you do anything about this? So, we worked with local MND Association branches to design a neck support for people living with MND."

The team trialled the new neck support, known as the Sheffield Support Snood, on 26 people living with MND, of which 20 completed the study.

Feedback from participants was that there was strong agreement that the Snood offered support, comfort and no pain compared to existing neck supports.

The next challenge for Dr McDermott is to get someone to make this and take this on, which is difficult due to the relatively small market. However, Dr McDermott stated that he is in the process of discussing this with several companies.

**Biomarkers**

The session featured a back-to-back presentation from Dr Andrea Malaspina (Queen Mary University of London) and Dr Martin Turner (University of Oxford), who have been pooling their expertise and resources to investigate a promising protein

biomarker called neurofilament light chain (NfL).

Measuring these proteins accurately is not an easy process, because damaged neurofilaments tend to clump together in blood and CSF in the same way that they do so in dying motor neurons, so Dr Malaspina and his team have spent several years refining and optimising the technique. He showed that samples from MND cases from both the Oxford and London collections could be discriminated from non-MND controls, with a sensitivity and specificity of over 95% for CSF samples.

Dr Turner said: "Neurofilaments are the building blocks of each and every nerve and are thought to accumulate in the spinal fluid (crossing over into the blood too) as nerves degenerate across a range of conditions. We have found them to be raised in people living with MND."

"Even though this finding in itself is not unique to MND, importantly the level seems to reflect an individual's speed of disease progression. What my group has been able to show (as part of BioMOx) is that this level can be directly linked to the damage we see in the motor tracts using the MRI scanner. It confirms that neurofilaments are objectively linked to the disease process in MND, and is a strong candidate for a workable biomarker that we might even be able to measure using only a blood test."

**Induced pluripotent stem cells and MND**

Dr Kevin Eggan started a session on induced-pluripotent stem cells (iPSCs), explaining that patients with MND have more electrically active neurones than people who are healthy. This can be shown using things like transcranial magnetic stimulation.

He wanted to investigate why motor neurones are more excitable, and he used iPSCs from two patients with a specific type of the SOD1 inherited form of MND.

When measuring the electrical activity of motor neurones from iPSCs, he found the same thing that he saw in people – that the SOD1-MND motor neurones have more activity compared to activity in healthy motor neurones.

Dr Eggan was using a new technique with an adapted pore within the motor neurones that is sensitive to blue light – when blue light is shone on the motor neurones the channels open and they become electrically active, what's more is that in his system, the presence of electrical activity causes a tag on another part of the nerve cell to glow red. Through this work he showed that the potassium brake on electrical activity doesn't work so well in the SOD1 form of MND.

**Therapy for SOD1 MND?**

With all the talk of new gene discoveries in recent years, the final day of the symposium returned to the original discovery in 1993 that mutations in the SOD1 gene were responsible for around a fifth of inherited MND cases and 2-3% of all cases of the disease.

Although much of our understanding of MND in the past two decades comes from SOD1 laboratory models of the disease, we still don't know exactly how SOD1 kills motor neurons. But that hasn't stopped several groups from working on a number of innovative ways of protecting motor neurons from SOD1 toxicity. Although focused on a relatively rare form of MND, some of the strategies being followed could potentially also be applicable to other forms of the disease.

Dr Loreiei Stoica from Massachusetts Medical School, explained that they are switching off the SOD1 gene by reducing the gene activity in the spinal cord of SOD1 mice by over a third, leading to a 50% increase in survival. However, some animals did show side effects that need to be explained before this approach can be considered for the clinic.

Dr Grad (University of British Columbia) has identified a part of the SOD1 protein structure that appears to be crucial for the propagation to occur. Using computers, he has started to design more 'drug-like' compounds for testing, based on a molecule called uridine, which he has found is able to reduce SOD1 propagation in lab studies. This is early stage work, but has the advantage that it does not necessarily rely on the drugs getting inside cells, although they still need to be designed to get from the blood into the central nervous system.

Overall the three day event covered some fantastic science, as well as some innovative developments in care practice. Next year the symposium will be held in Orlando in just under a year's time, and who knows what will be discussed then!

Read detailed reports via the MND Association's MND Research blog and our peer-to-peer blog ReCCoB

# PREVIEW SMi present their 15th Annual conference on... Pain Therapeutics

***Conference details:*** 18 & 19 May 2015, Holiday Inn Bloomsbury, London, UK.

*Reviewing current opportunities in the effective and safe management of pain at SMi's Pain Therapeutics conference.*

SMi's Pain Therapeutics conference returns to London on the 18th & 19th May 2015 with a two day intensive agenda highlighting the latest developments in pain therapeutics and offering attendees a unique platform to engage with KOLs and esteemed academia to learn the challenges and successes in the field of pain management.

With the increasing demand for new research techniques and a range of drugs to combat chronic pain syndromes, this conference will highlight key factors including personalised medicine for pain, biomarkers and CGRP receptor antagonists for migraine treatment. Attendees will learn about Grunenthal's latest screening approach for neuropathic pain and pain models and hear timely case studies from Merck and Afferent Pharmaceuticals along with latest updates on developments in targeting nerve growth factors and advances in the treatment of pain from leading, pharma, biotech and academic experts from the industry. The conference will also feature an interactive panel discussion on reviewing validity of animal models for chronic pain.

**Keynote Speakers**

Expert panel of speakers will include Dr Gregor Bahrenberg, Associate Scientific Director from Grunenthal, who will speak on Vesicular Glutamate Transporters (VGLUTs) as targets for neuropathic pain. Professor Alexander Oksche, Executive Director of Pharmacological Intelligence from Mundipharma will speak on day one, highlighting recent developments in opiods.

The conference will also feature a spotlight session on Nerve Growth (NGF) updates; Mark T Brown, MD, Executive Director, Tanezumab Clinical Program Leader for Osteoarthritis and Cancer Pain Studies, from Pfizer will speak on Update on Tanezumab, a monoclonal antibody inhibitor of nerve growth factor.

**Interactive workshops**

Delegates can also choose between two half day workshops, both held on 20th May 2015 in London: workshop A is on: In vitro techniques and models for pain drug development: "Clinical trial in a dish" in association with Imperial College London and workshop B is on: Healthcare Innovation - A patient centred approach, in association with Insight Consultancy.

Visit www.pain-therapeutics.co.uk for more information or contact
Magdalena Georgieva on telephone
+44 (0)20 7827 6148
Email on mgeorgieva@smi-online.co.uk

**Quote ACNR and save £150****

# Oxford Medical Management Course

***Conference details:*** 19-21 November, London, UK. ***Report by:*** Claire McCarthy, Neurology SpR, Addenbrookes Hospital, Cambridge, UK.

**What is it?**

A three day course covering the theory and practical aspects of management and leadership for doctors. The course is held in London and other sites across the UK.

This course is designed to cover the basic principles of good leadership and management for doctors. The course is run by enthusiastic trainers who from the beginning demonstrate respect for Maslow's 'hierarchy of needs' the principle of which is that individuals require their basic physiological needs to be met to learn effectively. The smart, comfortable hotel, endless supply of caffeinated beverages, sensible timetabling of sessions and tasty warm lunch all set the background for a productive day. As you would expect from this type of course brief, interactive tutorials are interspersed with sessions of group work. To my relief, rather than cringe worthy role play sessions, the group work involved time pressured tasks which effectively demonstrated the principles of time management and team work. In addition, there were lots of opportunities for indulgent self-reflection such as 'what is my management style?', 'am I task or people focused?' and 'how does my personality affect my approach to tasks?'. The third day was run by a doctor who covered the structure of the NHS, finance and change in the NHS.

> *Useful techniques for effective time management including the 'urgent-important time clock'*

**Who should do it?**

The course is most suitable for registrars approaching the end of their training and new consultants.

**Would you recommend it?**

Yes. Like it or not, all senior doctors have managerial roles and need to understand the structure and management framework of the NHS to drive forward the development of services for their patients. The course provided a useful approach to developing key skills such as conflict resolution, negotiation, implementing change, business case planning and managing teams. The course materials provided in depth information on the structure of the NHS which will prove invaluable for preparing for consultant interviews. The only drawback is the cost, at £599 for the three days it certainly isn't cheap but in my view the course does deliver an understanding of the world of management that is likely to prove invaluable in my future career.

**Key learning points:**

- Change is inevitable in large organisations like the NHS, good managers prepare an organisation for change and guide employees through it. The course teaches approaches to implementing change such as the SWOT analysis (identifying strengths, weakness, opportunities and threats) and explains that colleagues' reactions to change can be similar to a grief reaction.
- Useful techniques for effective time management including the 'urgent-important time clock'.
- Effective methods for setting objectives for yourself and others such as the SMART approach (Specific, Measurable, Achievable, Relevant and Timed).

# The changing landscape of the epilepsies – healthcare professionals conference

***Conference details:*** 24 October 2014, London, UK. ***Reviewed by:*** Anthony Linklater, epilepsy specialist nurse at the National Hospital of Neurology and Neurosurgery, London, UK.

Epilepsy Society and London South Bank University presented their second annual joint healthcare professionals conference on epilepsy. The focus of this year's conference was the changing landscapes of the epilepsies.

Professor Ley Sander, Epilepsy Society's medical director, delivered the first plenary at the event held at London South Bank University. He spoke about the paradigm shift in epilepsy from a model of treatment based on experience and observation to one based on a fuller knowledge of an individual's genetic profile and on a better understanding of the way in which different anti-epileptic medications work.

The genetic causes of epilepsy and what we are learning from research, was the crux of Professor Sanjay Sisodiya's plenary. The honorary consultant neurologist at Epilepsy Society gave examples of how genetic sequencing can help give certain patients an explanation of their condition. By recognising epilepsy syndromes, defining them genetically, they are beginning to be understood biologically. Researchers are moving from discovering genes that are responsible for epilepsy to applying that knowledge in clinical practice.

Professor Sisodiya said that currently one in three people visiting Epilepsy Society's Chalfont Centre left with a different diagnosis to the one they had had on arrival.

Differential diagnosis of non epileptic seizures was the plenary given by Dr Brent Elliot, Epilepsy Society's honorary consultant neuropsychiatrist. He said Non Epileptic Attack Disorder (NEAD) and Functional Neurological Disorder (FND) significantly affect the quality of life of both patient and carer. Adding that it's estimated that the annual health costs of patients presenting with NEAD symptoms is £18 billion, with treatment falling squarely in the gap between neurology and mental health commissioning.

Professor Philip Patsalos, the charity's consultant clinical pharmacologist spoke about the uses and benefits of therapeutic drug monitoring (TDM). He said his unit at Epilepsy Society's Chalfont Centre was the only one stop shop in the country for TDM and the only place in the UK to carry out saliva testing. He said monitoring drug levels in saliva can offer a convenient and painless alternative to taking blood samples when helping to optimise the level of epilepsy drugs on an individual basis.

Delegates also had the opportunity to attend two of four breakout sessions which covered:

- Service improvement for better outcomes, given by Juliet Ashton, Epilepsy Society's specialist epilepsy commissioning nurse consultant;
- Epilepsy and learning disability: risk management and capacity, by Jennifer Long, Epilepsy Society service manager;
- Supporting evidence for claims, given by Alban Hawksworth, Independent benefits specialist;
- The value of the pharmacist in the multidisciplinary team, given by Dr Trudy Thomas, Director of taught graduate studies, Medway School of Pharmacy.

The conference by Epilepsy Society and LSBU was both interesting and stimulating, with delegates reporting they had gained knowledge and insight into developments within epilepsy management.

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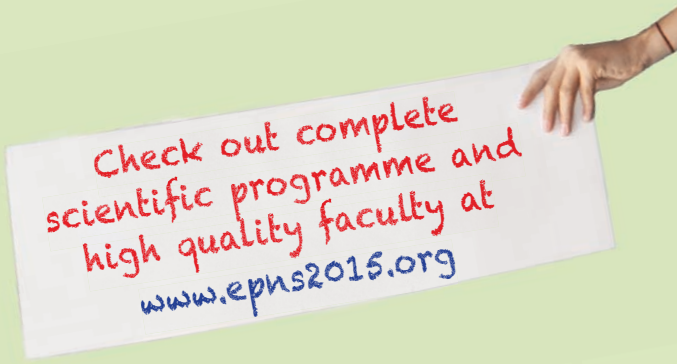


### Programme Highlights

#### Plenary Sessions

- Epilepsy surgery
- Fetal Neurology
- Inflammatory diseases of the nervous system
- Rett Syndrome – once and today
- Stroke

#### Parallel Sessions

- Ethics
- Highlights in Paediatric Neurology
- Language – Localisation and reorganisation
- Movement Disorders
- Neurological manifestations of TSC
- Neurometabolic Disorders
- Neuromuscular Disorders
- Neuropsychiatry
- Neuro-Rehabilitation & Future Techniques
- Preterm infants: Brain, morphology and function – long term follow-up
- Teaching Session:
  Sleep related movement disorders
- Teaching Session:
  Ketogenic Diet

### Specials

- Pre-congress Satellite Symposium:
  First EPNS International Symposium on Advances on Neuromodulation in Children (25–26 May 2015)
- Joint video conference Session with EACD (29 May 2015)
- EPNS Academy of Paediatric Neurology:
  Neuroimaging in Paediatric Neurology (30 May 2015)
- 11 Early morning sessions
- 90 Free paper presentations
- Over 400 e-posters
- 240 Poster short presentations
- Award ceremony
- 11 Industry symposia
- Varied industry exhibition
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