

# ACNR

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**ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION**

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Daily dosage should be given in 1-2 single doses. Contents of the capsule/sachet may be sprinkled or stirred into soft food or drinks (cold or room temperature) and swallowed immediately without chewing or crushing the granules. Changing from sodium valproate enteric coated tablets to Episenta®, keep the same daily dose. **Elderly:** Care when adjusting dosage. Dosage should be determined by seizure control. **Renal insufficiency:** May be necessary to decrease dosage. **Hepatic insufficiency:** see Contraindications, Warnings and Precautions and Undesirable effects. Salicylates should not be used concomitantly. **Combined Therapy:** Start Episenta® in patients already on anticonvulsants gradually. Target dose reached after about 2 weeks. 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Avoid concomitant salicylates in children <3 years. Salicylates should not be used in children <16 years. Measure liver function before treatment and during the first 6 months. Risk of severe or fatal pancreatitis, particularly young children; risk decreases with increasing age. Blood cell count, platelet count, bleeding time and coagulation tests recommended prior starting therapy before surgery, or if spontaneous bruising/bleeding. Caution in patients with systemic lupus erythematosus. Risk of hyperammonaemia in patients with urea cycle enzymatic deficiency. Risk of weight gain. Caution in women of childbearing potential. **Interactions:** Episenta® on other drugs: may potentiate psychotropics, e.g. antipsychotics, monoamine oxidase inhibitors, antidepressants, benzodiazepines. Increases phenobarbital concentrations which may cause sedation particularly in children. Increases primidone levels exacerbating side effects. 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Packs of 5, 3ml ampoules 100mg/ml solution for injection £35.00 [PL14040/0028]. **Legal category:** POM. **Marketing Authorisation Holder:** Desitin Arzneimittel GmbH Weg beim Jäger 214 D-22335 Hamburg Germany. **Prepared in:** July 2012. For further information on Episenta® please contact Medical Information on [MedInfo@desitin.co.uk](mailto:MedInfo@desitin.co.uk)

### References:

1. Episenta® Summary of Product Characteristics 2012.
2. Retzow A et al. *Arzneim-Forsch/Drug Res* 1997;47(II):1347-1350.
3. MIMS, July 2012.

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Desitin Pharma Limited on [MedInfo@desitin.co.uk](mailto:MedInfo@desitin.co.uk)



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Mike Zandi, Editor

In this issue, as a link to the ABN meeting in Glasgow at the end of May, Mark Edwards, from the Institute of Neurology, Queen Square, reviews mechanisms in the pathophysiology of functional movement disorders. The evidence for dysfunctional attention, the influence of prior beliefs and expectations, and the role of agency are each examined in this clear and helpful account. Mark Edwards reminds us that the language used to describe this group of disorders can negatively affect outcome. 'Psychological' factors are discussed but are de-emphasised. A remarkable property of the diagnosis of functional neurological disorders is the stability of the diagnosis over time and the low rate of misdiagnosis by neurologists, in particular if done on the basis of positive physical signs. Mark Hallett will speak on this subject in the 19th Gordon Holmes lecture at the ABN meeting in Glasgow. This is followed by a teaching session on functional disorders by Mark Edwards, Jon Stone and Alan Carson. Hallett and colleagues' book, *Psychogenic Movement Disorders (AAN, 2006)*, is recommended reading. Martin Rossor introduces the ABN meeting on page 11 of this issue and we also include the programme.

It is 40 years since Tim Bliss and Terje Lomo described LTP in the *Journal of Physiology* in 1973, and we were lucky enough to have an account of this discovery in *ACNR* last year by Terje Lomo (*ACNR* May/June 2012, p14-17). Olivia Shipton and Ole Paulsen from Cambridge, in the current issue provide a clear summary of recent advances in our knowledge of hippocampal plasticity and LTP, with a focus on recent work on NMDAR biology, structural changes in synapses and their measurement, and the evidence that any of this actually impacts on behaviour. It is clear that while the mechanisms behind memory are still not well defined, this work holds great potential in developing new treatments for a range of neurological diseases associated with dysfunction at the synapse.

Erica Chisanga from Cambridge writes in Mark Manford's epilepsy series, a clear account of how to approach the many issues of epilepsy in the elderly, in particularly dealing with therapeutic options and social aspects. Marianne Novak and Rumana Chowdhury in this issue's ABNT article provide helpful tips in securing a training number in neurology: an article to disseminate to your junior colleagues. Finally, Mark Baker from NICE provides a succinct one page summary of NICE's recommendations for the treatment of headache. We have our usual book, conference and journal reviews and collections of news, and hope you enjoy this issue of *ACNR*.

Mike Zandi, Editor  
Email: [Rachael@acnr.co.uk](mailto:Rachael@acnr.co.uk)

## New Marketing Manager at Fujifilm

Ben Cole is the new Marketing Manager at Fujifilm. Ben graduated from the University of Hertfordshire in 1998, with a BA (Hons) in Business Management, and has also undertaken a range of professional training, including gaining his Diploma in Marketing from the Chartered Institute of Marketing in 2006. Fujifilm is a pioneer in diagnostic imaging and information systems for healthcare facilities, with a range of constantly evolving clinically proven products and technologies designed to assist medical professionals perform more efficiently and effectively.



Ben brings a wealth of experience to Fujifilm, acquired from his time spent with three blue chip healthcare companies.

## Franz Gerstenbrand Award

The WFNR has launched the Franz Gerstenbrand Award for clinicians, researchers and allied health professionals to recognise and reward a neurorehabilitation project that has benefited patients. Named after Professor Franz Gerstenbrand, in recognition of his continuous contributions to neurorehabilitation, the Award is open to WFNR members and non-members worldwide. Entries can come from any aspect of neurorehabilitation and examples include a patient or clinic management initiative, research project, best practice development or the use of a new technological development.

For more information [E.traceymole@wfnr.co.uk](mailto:E.traceymole@wfnr.co.uk), or see [www.wfnr.co.uk](http://www.wfnr.co.uk)

## Nominations for UKABIF Awards 2013

Nominations are invited for the two prestigious United Kingdom Acquired Brain Injury (UKABIF) Awards – the UKABIF Award for Innovation and the UKABIF Award for Inspiration. Both are open to people working in the field of acquired brain injury (ABI). Deadline for entries is 18th October 2013.

The UKABIF Award for Innovation is open to individuals or organisations that make a difference in ABI: a lawyer/law firm, clinician, care provider, social care worker, educational or voluntary sector provider or a registered charity. The innovation can be a new invention or an improvement, for example, to an existing service.

The UKABIF Stephen McAleese Award for Inspiration is for an individual in the field of ABI who has taken the lead and prompted action or invention.

More information from [www.ukabif.org.uk](http://www.ukabif.org.uk)

## Medical Student Essay Prize & Travel Bursary

The Encephalitis Society invite UK under- and post-graduate medical school students to participate in the Medical Student Essay Prize. A prize of £500 will be awarded for the best medical student essay on any aspect of Encephalitis. Submission deadline is 1st October 2013. The winner and runner-up will be announced at The Society's Professional Panel meeting on the 2nd December 2013, in London, and will be required to present their essay at the Society's professional panel meeting in December 2014. UK medical school students are also invited to apply for the Society's Medical Student Travel Bursary.

More information from [www.encephalitis.info](http://www.encephalitis.info) or [E.ava@encephalitis.info](mailto:E.ava@encephalitis.info)

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Cover picture: Project Ability is a visual arts charity supporting people with learning disabilities, adults in recovery from mental illness and children and young people with disabilities to develop their creative practice. In 2011 the SECC commissioned Project Ability artists to produce art work in response to the SECC; its function, geography and architecture. This painting "A summer's evening" is by William Smith.

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# Hippocampal Plasticity – An Update



## Olivia Shipton

is a final-year DPhil student on the Wellcome Trust-funded Oxford Ion Channels and Disease Initiative (OXION). She is interested in the role of hippocampal plasticity in learning and memory, and its impairment in Alzheimer's disease.



## Ole Paulsen MD/PhD

is the Professor of Physiology (1883) at the University of Cambridge. He is interested in the relationships between network architecture, circuit dynamics and synaptic plasticity in health and disease.

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It is now forty years since the first full report of long-term potentiation (LTP), a presumed cellular substrate for learning and memory. This short review will provide an update on some recent advances in our understanding of the mechanisms underlying hippocampal LTP and address their potential clinical relevance.

### Introduction

The hippocampus plays a fundamental role in learning and memory processes, as famously discovered with the study of patient HM, who lost the ability to lay down new memories after surgical removal of the medial temporal lobes.<sup>1</sup> Not only is the hippocampus necessary for memory formation, it is also activated during memory tasks (Figure 1). The acquired information is thought to be stored as changes in the connections between hippocampal neurons and such changes are known as synaptic plasticity, the strengthening and weakening of synaptic efficacy. The best-described hippocampal plasticity process is that of long-term potentiation (LTP), which will be discussed here.

Forty years ago, Bliss and Lømo reported that a high-frequency train of presynaptic stimulation in the rabbit hippocampus *in vivo* caused strengthening of the postsynaptic response to a given stimulation,<sup>2</sup> confirming earlier suggestions about activity-driven synaptic changes proposed independently by Konorski (1948)<sup>3</sup> and Hebb (1949)<sup>4</sup>. This “long-lasting potentiation” is now known as LTP and has received much experimental attention over the years due to the widely held view that it could be a cellular substrate for learning and memory. Initial exploratory research confirmed that LTP was found in other animals, other hippocampal pathways and brain regions, and even in *in vitro* brain slice preparations, which proved particularly important for further detailed experimental dissection.

Thirty years ago, a fundamental step forward was made in our mechanistic understanding of LTP with the demonstration of NMDA receptor (NMDAR) involvement.<sup>5</sup> Upon activation by synaptically-released glutamate, NMDARs open an ion channel permeable to Ca<sup>2+</sup>, required for LTP.<sup>6</sup> Ten years later, Bliss and Collingridge summarised the intracellular pathways of plasticity that had been uncovered so far and outlined a number of crucial unresolved issues in their seminal review.<sup>7</sup> So how far have we come in answering them?

### Major recent advances

The long-established mechanism of hippocampal LTP involves the presynaptic release of glutamate along with a postsynaptic depolarisation sufficient to relieve the NMDAR of its Mg<sup>2+</sup> block. The ensuing

Ca<sup>2+</sup> influx through NMDARs can then trigger downstream kinase cascades that cause the increased recruitment of AMPA receptors (AMPA) to the postsynaptic membrane, which supports the initial increase in synaptic strength. In the longer term, changes in synaptic strength are maintained by synaptic remodelling. Significant progress has been made in our understanding of the mechanisms underlying the induction, expression and maintenance of synaptic plasticity.

### Induction

The necessity of NMDARs for the induction of hippocampal LTP is unrefuted; indeed, the crucial feature of LTP induction protocols is that they cause sufficient depolarisation to permit a high level of Ca<sup>2+</sup> influx through these NMDARs. The induction protocols most commonly used are high-frequency (“tetanic”) stimulation (Figure 2), theta burst stimulation and pre-postsynaptic spike pairing. The latter paradigm induces spike timing-dependent potentiation (tLTP),<sup>8</sup> which confirms Hebb's prediction that potentiation occurs when the presynaptic neuron takes part in firing the postsynaptic neuron.<sup>4</sup> tLTP is, therefore, an attractive model for learning as these precise timing requirements of neuronal activity indicate a mechanism for encoding associations in the external world. NMDARs comprise four subunits, two obligatory GluN1 subunits and two additional GluN2 subunits, of which there are different types. It is increasingly recognised that GluN2B subunit-containing NMDARs are required to support LTP,<sup>9</sup> most likely because of the tight association between the GluN2B subunit and Ca<sup>2+</sup>/calmodulin-dependent protein kinase II, which has been identified as a crucial enzyme in LTP induction.<sup>10</sup> Interestingly, GluN2B subunit-containing NMDARs may be particularly vulnerable to, and help mediate, the synaptotoxic effects of amyloid beta,<sup>11</sup> and so further understanding the unique role they play at the synapse and in LTP could help with treatment of neurodegenerative diseases that affect learning and memory.

### Expression

It is well established that a greater number of AMPARs at the postsynaptic membrane supports the increased synaptic strength in LTP. This process involves initial recruitment of GluA1 subunit-containing AMPARs to the postsynaptic membrane and their subsequent replacement by GluA2-containing AMPARs to support a continued enhancement of synaptic strength.<sup>12</sup> However, the mechanism has recently emerged as more complex than simply direct insertion of AMPARs at the postsynaptic site, and instead it appears that a three-stage model may explain this increase.<sup>13</sup> Firstly, LTP triggers exocytosis of GluA1-containing AMPARs to

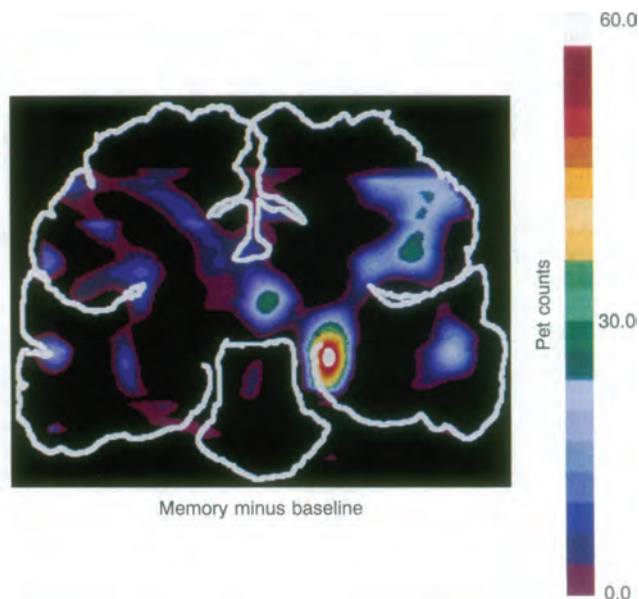


Figure 1: The human hippocampus is activated during a memory task involving word recall. Note the asymmetry, such that only the right hippocampal formation shows activity greater than baseline levels. Reproduced with kind permission of Larry Squire (from ref. 28).

extra- and peri-synaptic regions; secondly, these diffuse laterally into synaptic sites; thirdly, receptors must be captured by the scaffolding of the postsynaptic density in order to be maintained at the synapse. Although LTP pathways likely exert tight regulation of the initial membrane insertion stage, a recent paper suggests that the subsequent steps of this process may be more flexible. Granger *et al.* found that, although a reserve pool of receptors was required to support synaptic strengthening in the hippocampus, the subtype identity of the AMPARs was unimportant; moreover, even the kainate receptor, a glutamate receptor not normally found at that synapse, could substitute.<sup>14</sup> Although this research was conducted with endogenous AMPARs deleted, this newly found flexibility at the synapse has implications for the clinic, since it opens the door to the introduction of new designer receptors to restore synaptic function in neurodegenerative conditions. However, this lack of specificity is a double-edged sword, since perturbing this process at a synapse could have many unforeseen consequences.

### Maintenance

It has been suggested that LTP is maintained by persistent kinase activity. A strong candidate for this role appeared to be a kinase known as PKM $\zeta$ , since blocking it with a peptide called ZIP reversed both hippocampal LTP and specific spatial memories.<sup>15</sup> However, the importance of this 'memory molecule' has recently been questioned as two labs have reported that hippocampal LTP and hippocampus-dependent learning are present in both constitutive and conditional PKM $\zeta$  knock-out mice.<sup>16,17</sup> In fact, it seems unlikely that a mechanism merely involving elevated kinase activity could maintain information storage over years, and a better candidate to sustain enhanced synaptic strength would be structural changes at the synapse. Imaging in neuronal cultures and in animals *in vivo* has revealed two major structural changes associated with LTP. Firstly, pre-existing thin postsynaptic spines enlarge.<sup>18</sup> Secondly, new spines appear, and LTP also correlates with the stabilisation of such nascent spines.<sup>19</sup> When spines enlarge sufficiently they become known as mushroom spines; chronic imaging has revealed that spines of this type can be stable for months<sup>20</sup> and are not permanently changed following an LTP protocol,<sup>18</sup> suggesting they may be robust to perturbations and hence able to act as a 'memory store'. The positive correlation between the volume of the posterior hippocampi of London taxi drivers and the length of time spent in this hippocampally-demanding career is an indication, although not without alternative interpretations, that long-term structural changes also exist in humans.<sup>21</sup>

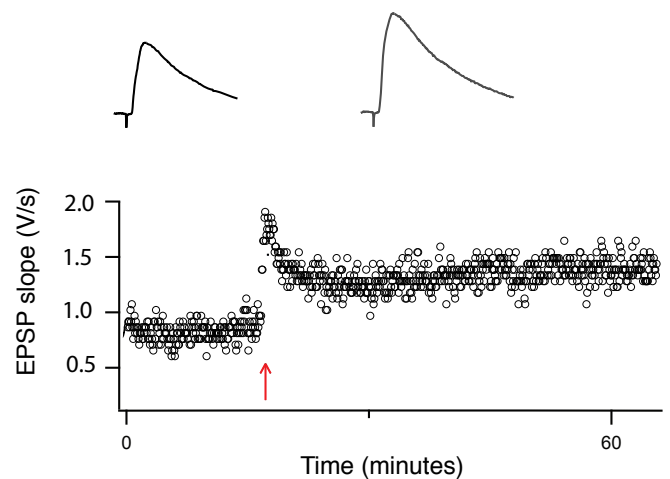


Figure 2: Hippocampal long-term potentiation (LTP). Excitatory postsynaptic potentials (EPSPs) are monitored over a baseline period (top panel, left) and then a specific induction stimulation paradigm is applied (red arrow). Following tetanic stimulation, an immediate post-tetanic potentiation is seen, followed by a long-lasting increase in the magnitude of the EPSP (top panel, right) that represents a strengthening of synaptic efficacy.

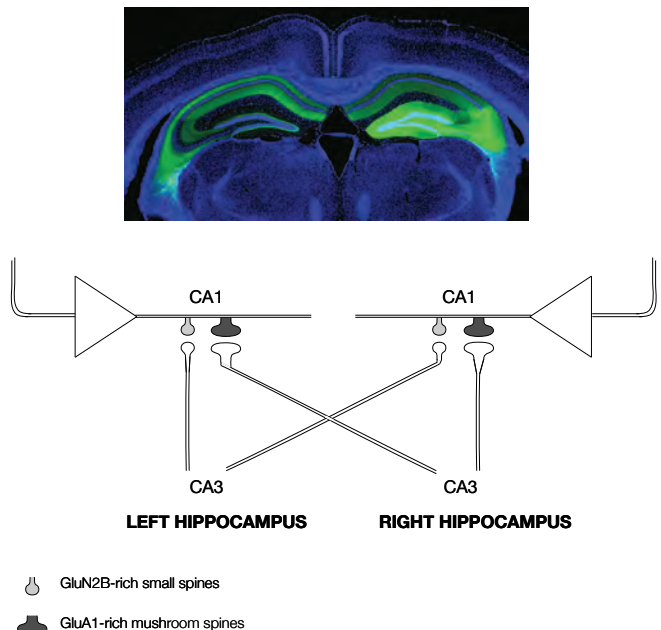


Figure 3. Excitatory neurons of the left and right CA3 region of the hippocampus project both ipsilaterally (Schaffer collaterals) and contralaterally (commissural connections) to pyramidal neurons of the CA1. These excitatory projections from CA3 pyramidal neurons to the CA1 can be selectively targeted by stereotaxic injection of an optogenetic construct into the CA3 of one hemisphere (top panel: image depicts a right injection; green: fluorescent tag expressed from the optogenetic construct; blue: nuclear stain). In mice, the nature of the CA1 spine is dependent on the location of the presynaptic CA3 neuron from which it receives its input. CA1 spines receiving input from CA3 neurons in the left hippocampus are small spines that are GluN2B-rich. Conversely, CA1 spines receiving input from CA3 neurons in the right hippocampus are large, mushroom-shaped spines that are rich in AMPA receptors (bottom panel). Only those synapses that receive left CA3 input express tLTP, and this correlates with the distribution of GluN2B subunit-containing NMDA receptors.

### Plasticity and behaviour

A major challenge for the future is to understand the relationship between plasticity and behaviour. Although the implicit and explicit assumption has been that plasticity supports memory,<sup>22</sup> we still only have correlative evidence for this assertion, and, combined with the recent finding that NMDARs in the CA1 are not always necessary for hippocampus-dependent learning and memory,<sup>23</sup> it remains unresolved. A newly developed technology, known as optogenetics, which allows acute control of neuronal activity in regionally- and genetically-defined cell populations by light, may help probe a causal link between plasticity and memory. This has already been used at the cellular level to show that

reactivating neurons in the dentate gyrus of the hippocampus that were active during acquisition of fear conditioning triggers expression of the context-dependent fear memory.<sup>24</sup> The next stage is to investigate the relationship between plasticity and behaviour at the level of synapses. One promising model to investigate whether distributed changes in synaptic weights can support learning and memory may be the synapse between the excitatory neurons of the CA3 and CA1 regions in the mouse hippocampus. Here, an unexpected asymmetric distribution of postsynaptic spine types has been found whereby spines in CA1 neurons that receive input from the CA3 of the left hippocampus are mostly small and rich in GluN2B subunit-containing NMDARs, while those receiving right CA3 projections are larger and rich in AMPARs<sup>25</sup> (Figure 3). Due to this hemispheric asymmetry, these different types of spines can be targeted optogenetically and it was found that only the GluN2B-rich spines receiving left CA3 input show tLTP.<sup>26</sup> It is now possible to manipulate these two types of synapses with their different propensity for plasticity to test whether they have differential effects on learning and memory in behaving mice.

### Clinical relevance

Synaptic dysfunction is a central component of a wide range of neurological conditions. Understanding the basic mechanisms involved in hippocampal LTP may make it possible to alter plasticity and neural networks in predictable ways, and the hope is that this could be used therapeutically in the future. For example, the early stages of Alzheimer's disease are characterised by synapse loss in the hippocampus and the inability to lay down new memories. Using our greater understanding of the types of NMDARs and AMPARs involved in LTP induction and expression respectively, it might be envisaged that the synapse could be modified to prevent the initial synaptotoxicity and consequent neurodegeneration at early stages of the disease, or adapted to restore plasticity to remaining synapses later in the condition. One way to modify synapses to this end may be the introduction of NMDARs with a higher potential for LTP. Alternatively, so called 'designed receptors exclusively activated by designer drugs' (DREADDs) could be used. This novel pharmacogenetic technology involves stereotactic delivery of viral constructs containing DREADDs under specific promoter control so that engineered receptors are expressed by one type of neuron in a limited brain region, and then can be activated on demand by administration of a

designer drug to stimulate their function, for example to enhance plasticity. It is also conceivable that downstream kinases could be targeted, but these may have more non-specific effects on cellular processes and so be less amenable to manipulation. Of course, the ability to restore learning without eradicating old memories is a huge challenge, but further study of the mechanisms that generate and maintain the aforementioned hippocampal asymmetry in the distribution of synapses with different propensities for plasticity could provide insight into how we may hope to achieve this in the future.

The possibility of genetically altering synaptic receptor composition in discrete brain regions has broader clinical ramifications than treating diseases of synaptic dysfunction. The ability to 'reopen' a brain region for plasticity may be particularly useful in aiding recovery from stroke or brain injury. Moreover, since both optogenetics and DREADDs enable the stimulation or suppression of activity in specific neuronal populations and circuits, they might prove a desirable replacement for deep brain stimulation in the treatment of Parkinson's disease and depression. They could also be developed to treat obsessive-compulsive disorder, addiction and otherwise intractable epilepsies. For example, it was recently shown that both optogenetic and K<sup>+</sup> channel gene therapy were successful treatments in a rat model of focal neocortical epilepsy.<sup>27</sup> Pharmacogenetics is a particularly appealing approach as, apart from the initial stereotactic surgery, it would be less invasive than chronic implantation of electrical or optical stimulation devices. Nevertheless, the ability to manipulate neuronal circuits at such a finely tuned level also brings with it many ethical considerations.

### Conclusions

Huge advances have been made in the forty years since LTP was first formally described, though we are still unravelling the complexity of the various mechanisms of induction, expression and maintenance that support synaptic strengthening. The biggest scientific question in the field of whether or not LTP is the memory mechanism, remains unanswered. Excitingly, novel technologies now make it possible to test a causal relationship to definitively answer this question, and, moreover, probe how exactly plasticity supports learning and memory. Furthermore, there is potential scope to harness our current knowledge for therapeutic purposes, not only in disorders affecting learning and memory, but also to enhance recovery following brain injury. ♦

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# Mechanism of Functional Neurological Symptoms



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**What's in a name?**

Words used to describe patients with functional neurological symptoms suggest either that we know clearly what the mechanism is (psychogenic, psychosomatic, conversion disorder), or that we have no idea (medically unexplained). Added to this is a pervasive colloquial use of terms in doctor-to-doctor communication about patients with functional neurological symptoms which betrays a considerable ambivalence as to whether there is any difference between their symptoms and feigned illness: "Are the seizures real?", "Did you think there was a genuine weakness?"

The confident use of terms such as 'psychogenic' to describe patients with functional neurological symptoms suggests a misplaced confidence in dichotomising physical and psychological processes, when the neuroscientific reality is that such processes cannot be separated. Even if one believes that the psychological level is the best level on which to understand the problem of patients with functional neurological symptoms, simply declaring that the symptoms are 'psychological' absolutely fails to account for the mechanism of symptom production in the brain. Perhaps this is why it is easy to slip from this to also using terms such as 'real' or 'genuine', something which fits with common patient and societal perceptions<sup>1</sup> that use of the psychogenic/psychosomatic label is similar to saying symptoms are wilfully 'put on'.

One way forward could be to start with a simple question: what it is about the symptoms and signs presented by patients with functional symptoms that allows neurologists to make the diagnosis with such a low rate of misdiagnosis<sup>2</sup> at long-term follow-up? It is most helpful to start to consider this question with regard to patients with functional motor symptoms, as the objective way in which the diagnosis can be made in these patients is very clear. Functional symptoms very commonly co-occur, and so there is highly likely to be generalisability from mechanism of production of functional motor symptoms to other functional symptoms such as functional non-epileptic attacks and functional sensory disturbance.

The diagnosis of functional motor symptoms, when done correctly, is not based on the presence or absence of psychological stress or difficulty, but on positive physical signs. Thus Hoover's sign and distractibility of tremor demonstrate a key role for attention in generating symptoms: when attention is distracted movement normalises. Put simply, the dependence on attention for movement production makes such movements look voluntary. The only thing, clinically, that separates patients with such symptoms from those who are feigning symptoms is the self-report of agency: patients with functional motor symptoms describe them as involuntary and out of their control. Another important feature of functional symptoms is that they can often be shown to fit with lay beliefs about how the brain might work, rather than what is known from basic neuroanatomy

and physiology. An example of this phenomenon is a tubular visual field defect, where the visual field defect is the same size close to the patient or far away, something that defies the laws of optics.

Following this logical argument, we then have three key processes, well known from decades of neuroscientific study, which are implicated in the pathophysiology of functional symptoms and which are amenable to experimental investigation: attention, belief (in the sense of prior expectations/internal models of the world) and agency.

**Attention**

Clinical signs in patients with functional neurological symptoms show clearly the importance of self-directed attention in generation of symptoms: when distracted, patients are typically much less symptomatic. Conversely it is very easy to generate new symptoms and worsen existing ones during clinical examination, most likely via enhancing self-directed attention. This phenomenon has been studied experimentally, with evidence that duration of direct visual attention towards the body during movement (e.g. looking directly at the limb which is moving) is significantly higher in patients with functional motor symptoms than neurological disease controls.<sup>3</sup> In patients with functional motor symptoms, movement is abnormal when explicitly cued as is motor learning in an explicit context.<sup>4,5</sup> However, movement is normal when cued implicitly as is implicit motor learning (e.g. learning a visuomotor transformation).<sup>5</sup> These data fit also with the results of some of a very mixed field (in terms of patients studied and paradigms used) of functional imaging studies in functional neurological symptoms. A number of such studies (see 6 for a review) show differences in activation of prefrontal regions during attempted movement which are similar regions to those engaged when healthy people pay attention to the production of overlearned movement patterns<sup>7</sup> (a process which in healthy people impairs movement production). The basic point here is that attention towards the mechanics of movement production and otherwise monitoring internal bodily sensations is an abnormal state, and may directly interfere with normal movement production and sensory perception.

**Beliefs, expectations and internal models of the world**

The idea that beliefs about ourselves and our health can alter perceptual experience and movement is not new: this is the basis of placebo effects and hypnotic suggestion. However, the combination of prescient work by 18th and 19th century scientists Thomas Bayes and Herman Helmholtz and modern cognitive neuroscience has moved 'beliefs' (in the sense of predictions or expectations about the world) to the centre of an idea of how the brain works. In these models, the brain is an inference machine, constantly making predictions about

expected sensory data and comparing it with actual sensory data received from the environment.<sup>8</sup> Via interactions of this sort at multiple reciprocally connected levels, a percept arises which combines varying contributions of actual sensory data and expectations about that data. Importantly, this mix is not fixed, and depends on the weighting of expectations over sensory data: this is why perception is so malleable depending on context. This same process is proposed to account for movement too, and therefore provides a potentially neurobiologically sound foundation to build a neurobiological model of functional neurological symptoms on. In one study relevant to this, patients with functional and organic tremor were asked to wear a 'tremor watch' which recorded tremor constantly.<sup>9</sup> They were in parallel asked to fill in a diary reporting how much of the day they felt they were affected by tremor. Both groups of patients over-estimated the amount of the day they experienced tremor (i.e. perception was more in line with expectations than sensory data), but those with functional tremor did this to a significantly greater extent than patients with organic tremor: on average they had only 30 minutes of tremor a day while reporting tremor 80-90% of the time. As the nature of the study was made explicitly clear to participants, malingering seems an unlikely explanation. An alternative explanation is that whenever attention was turned towards the limb in patients with functional tremor, tremor was generated, and that expectations/predictions relating to the presence of constant tremor was so strong that it overwhelmed any sensory feedback that should have indicated absence of tremor during periods when attention was diverted. In a more abstract study of belief formation under conditions of uncertainty, patients with PMD demonstrated a 'jumping to conclusions' style of decision making.<sup>10</sup> This decision making pattern, making a decision on the basis of limited evidence, has previously been reported in patients with delusions, and makes a potentially interesting link between functional symptoms and perceptual distortions that occur in neuropsychiatric illness.

### Agency

Agency relates to the subjective sense that a movement (for example) was self generated and did not just 'happen'. Patients with functional tremor scanned during their habitual tremor and periods when they deliberately mimicked their tremor were found to have reduced temporoparietal junction (TPJ) activity during their habitual tremor.<sup>11</sup> The TPJ is a key node in the network that is thought to mediate comparison between sensory data from the body and expectations/predictions about that data. The hypoactivity found in patients was interpreted as reflecting the lack of an appropriate sensory prediction signal that one would usually associate with voluntary movement, and hence could explain why functional movement symptoms, while looking voluntarily generated, are not experienced as such by patients. This is in keeping with a subsequent behavioural study showing a lack of the normal feeling of intention to move before a voluntary movement in patients with psychogenic tremor.<sup>12</sup>

### Putting it together

So where does this leave us in our understanding of mechanism of functional neurological symptoms? A number of proposed models<sup>13-15</sup> highlight the aetiological importance of the natural flexibility that exists in the brain regarding the way that sensory information about the state of the body and expectations/predictions about these data are integrated to produce our perceptual experience and action. The crucial first step in the production of functional symptoms is therefore proposed to be the instigation of an abnormal belief/expectancy relating to the symptom(s). This suggestion is at the heart of a number of proposed models for the generation of functional symptoms.<sup>13-15</sup> It is of note that the instigation of this belief/expectation could arise from a number of different factors (which could be different in different people) including emotionally traumatic events, but also physical triggering events (injury, organic illness) that are commonly reported around onset and panic responses associated with such events (also commonly reported) which could serve to increase the salience of the novel sensory data coming from the physical event. The second step required for symptom generation is simply activation of this 'rogue representation'<sup>13</sup> / 'previously mapped conversion motor representation'<sup>14</sup> / 'abnormal intermediate level prior'.<sup>15</sup> Here there may well be a role for abnormal limbic system activation,<sup>16</sup> and also for self-directed attention. The last step in the model is that activation of the 'rogue representation'<sup>13</sup>

is not accompanied by the normal neural 'baggage' that accompanies voluntary movement or normal sensory experience, and hence it is mis-attributed by the patient as being a symptom and out of their control.

### From Mechanism to Treatment...and Clinical Responsibility

Much of the debate about aetiology of functional neurological symptoms focuses on factors such as childhood or recent emotional trauma, anxiety, depression and personality disorder, and hence these factors are often considered of prime (perhaps sole) importance in treatment. Maybe this is why neurological practice is commonly to make the diagnosis of 'no neurological disease' and hand the patient back to primary care or on to mental health services. Epidemiological research suggests, however, that while such 'psychological' factors are present at higher rates in patients with functional neurological symptoms than the general population, that many, perhaps even the majority of patients are unaffected.<sup>17</sup> The discussion of mechanism above does not rule out a role, perhaps a very important one for such factors, but it is within a much richer aetiological context that is likely to be different for different people. In some patients, a simple biological understanding of how symptoms are being generated and physical and/or cognitive intervention directly informed by this understanding is the most effective form of treatment.<sup>18</sup> If there are continuing underlying psychological issues that may increase the chance of relapse of symptoms then direct treatment of these is likely to be important too. In patients with severe symptoms, these processes may need to be carried out in parallel as part of multidisciplinary specialist rehabilitation. However, for many patients, focusing on the 'how' rather than the 'why' of symptoms is more productive, more important, and ultimately more relevant for recovery than an exhaustive trawl through previous life events. In the end this is just about truly applying an individually flexible biopsychosocial model of care. Importantly, this implies that it is the neurologist who is the key person in diagnosis, explanation and coordination of treatment. Patients with functional neurological symptoms deserve a neurologist-led and properly supported service which is flexible to their differing needs regarding treatment. This is what we expect for our patients with neurological disease and we should expect no less for our patients with functional symptoms. ♦

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# Association of British Neurologists Annual Meeting

21 May – 24 May 2013 The SECC, Glasgow

## A welcome from the ABN President...

We are looking forward to welcoming delegates to the 2013 ABN Scientific Meeting at the Scottish Exhibition and Conference Centre, Glasgow.

For 2013 we have extended our usual teaching and science remit to include a session for GPs and medical trainees on the first day of the conference. Entitled 'Need to Know' Neurology, we hope to repeat the format at future annual conferences if the initial session proves successful. As in previous years, the first day will also feature our Medical Students' Roadshow and the ABN Trainees' study day.

The main Teaching and Science sessions will be focused on Headache, Functional Disorders, Stem cells in Neurology and Dementia. We have included a series of short updates on other neurological topics, invaluable for both clinical and academic neurologists, in the final session on Friday. The programme will also include the ever popular Neuro-ophthalmology, Video session (on Movement and Functional Disorders) and CPC.

May 2013 is the European Month of the Brain. In support of the awareness campaign our meeting has been formally badged as an EMOB event and there will be a public lecture aimed at schools on the Tuesday evening.

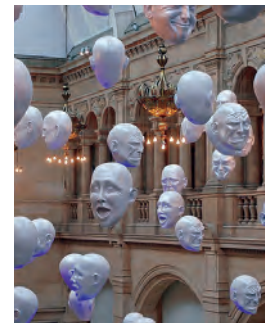
The following day we are delighted that Professor Mark Hallett, supported by the Guarantors of Brain, will deliver our 19th Gordon Holmes lecture 'The Pathophysiology of psychogenic movement disorders with musings on the nature of volition'. Later that day we are fortunate that Professor Jacques Prenderis, Professor of Comparative Neurology at The University of Glasgow School of Veterinary Medicine, has also accepted our invitation to give a lecture provisionally entitled 'Thereby hangs a tail – the neurology of Man's Best Friend'.

We have had the usual tremendous response to our call for abstract and papers. The resultant presentations and poster sessions promise to be both informative and thought provoking.

The Annual General Meeting will be held on Thursday 23rd at 4pm and the conference dinner will be at the Kelvingrove museum (pictured right).



Prof Martin Rossor



Association of British Neurologists Annual Meeting 2013  
An Eisai-sponsored interactive satellite symposium:

## When should an epilepsy patient be referred to an epilepsy specialist?

Wednesday 22nd May 2013, 12.30–14.00

The Boisdale Room, The Scottish Exhibition and Conference Centre (SECC), Glasgow

International faculty including Chair:

**Dr John Craig**, Consultant Neurologist,  
Belfast Health and Social Care Trust, UK



We invite you to attend this Eisai-sponsored satellite symposium on when an epilepsy patient should be referred for specialist care. As part of this interactive discussion, we would welcome your input ahead of the conference by filling out a short pre-event questionnaire, accessed below:

[www.surveymonkey.com/s/Eisai2013](http://www.surveymonkey.com/s/Eisai2013)



This satellite has been organised and funded by Eisai  
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## Open your mind!



## European Month of the Brain

May 2013

#brainmonth

An initiative of the of the

## Supercomputer – the brain and what happens when it crashes

This year's ABN starts with a special free lecture, delivered by out-going president Prof Martin Rossor on the body's own super computer – The Brain. Open your mind! May is the European Month of the Brain: the month in which to raise awareness of the importance of the brain and the diseases which can affect brain function. Neurologists specialise in understanding and treating the brain related disorders which will affect 1 in every 3 of us during our lifetime. This public lecture, which is arranged by the ABN, will explore what we have learned about the brain from studying brain disease, and how we can diagnose and treat, using molecules, micro-surgery, and machines. This one hour lecture takes place at the Island Suite of the Crown Plaza Hotel (next to the SECC) on Tuesday May 21st at 6.30pm. It will be a student-friendly exciting session and we would love local schools and colleges to get on board with us and bring their students along. Spaces are limited and so tickets need to be booked in advance. You can reserve multiple tickets at once under the one name, to make this process quicker.

Book at <http://www.eventbrite.co.uk/event/6525043581#>

## Tuesday 21 May 2013

<b>Neurology Road Show for Medical Students &amp; Foundation Year Doctors</b> <b>Chairs: Ian Ormerod, Biba Stanton</b>		<b>Specialist Registrar Session Sponsored By Merck Serono</b> <b>Chairs: John Paul Leach, Tracey Baird</b>	
1300	Welcome and introduction - Ian Ormerod	1300	Difficult consultations for trainees (small group teaching) - John Paul Leach, Philip Smith, Colin Mumford
1305	What do neurologists do - Geraint Fuller	1400	Managing peripheral nerve disease (small group teaching) - Mary Reilly, Lionel Ginsberg, Gareth Llewelyn, James Overell
1330	Training to be a neurologist - Biba Stanton		
1350	What do neurophysiologists do - Arup Malik	1530	<b>Tea break</b>
1420	Student presentations		
1520	<b>Tea break</b>	1600	The NMJ for neurologists - Arup Malik
1540	Small group teaching: how to think like a neurologist - Philip Smith, Geraint Fuller, Biba Stanton, Ralph Gregory	1630	Balancing your career with family life - Tracey Baird
1640	How to get involved in research - Cathie Sudlow	1650	The drug pipeline discovery – Clinical project manager Merck Serono
1710	Panel discussions - Cathie Sudlow, Geraint Fuller, Ralph Gregory, Biba Stanton		
1730	Quiz - Jonathan Schott	1730	Quiz – Jonathan Schott
1800	Reception and light refreshments		
1830-1930	<b>Month of the Brain Lecture - Martin Rossor</b>		

## Wednesday 22 May 2013

0730-0830	<b>Breakfast Satellite Symposium - Novartis: Brain Atrophy in MS – A marker in clinical practice? Followed by two debates</b>		
0900-0915	<b>Opening - Martin Rossor</b>		
0915	<b>Headache:</b> Advances in pathophysiological understanding of cluster headache – Phillip Holland, Edinburgh Update on management of migraine and cluster headache (medical and surgical) – Manjit Matharu, London New onset chronic daily headache - Alok Tyagi, Glasgow		
1045	<b>Coffee &amp; Exhibition</b>		
1115	Keith Muir Glasgow	Audit/Training – Richard Davenport Edinburgh, Paul Jarman London	
1245-1345	<b>Lunch &amp; Exhibition</b> <b>Lunchtime Symposium – Allergan: Spectrum of Headaches</b> <b>Lunchtime Symposium – Eisai: Debate: When should an epilepsy patient be referred to an epilepsy specialist</b>		
1400	<b>19th Gordon Holmes Lecture:</b> <b>Mark Hallett ‘The Pathophysiology of psychogenic movement disorders with musings on the nature of volition’</b> <b>Supported by the Guarantors of Brain</b>		
1445	<b>Teaching session 2 – Functional Disorders</b> Assessment of patient with functional disorders – Mark Edwards, London How to discuss the diagnosis – Jon Stone, Edinburgh Management of functional disorders – Alan Carson, Edinburgh		
1615	<b>Coffee &amp; Exhibition</b>		
1645	<b>PD/PRION</b>	<b>General neurology</b> – Bill Gibb Southampton, Colin Mumford, Edinburgh	
1800	<b>Plenary Lecture: Jacques Penderis, ‘Thereby hangs a tail – the neurology of Man’s Best Friend’</b> Professor of Comparative Neurology, University of Glasgow, School of Veterinary Medicine Chair – Geraint Fuller		
1900	<b>Welcome reception/Cognitive Neurology Section (Hall B)</b>		
2000	<b>ABNT Dinner</b>		



# **DEVELOPMENTS AND DEBATES IN NEUROLOGY – AN EDUCATIONAL FORUM**

**A NOVARTIS – SPONSORED SATELLITE SYMPOSIUM  
AT THE ASSOCIATION OF BRITISH NEUROLOGISTS (ABN) ANNUAL MEETING 2013**

**Wednesday 22nd May 2013**

**07:30 – 08:45**

**Alsh room, The SECC, Glasgow, Scotland**

## **Agenda**

**07:30 – 07:35**

### ***Welcome and introduction***

Siddharthan Chandran

**07:35 – 07:45**

### ***The consequences of not identifying and controlling disease activity in MS***

Siddharthan Chandran

**07:45 – 08:10**

### ***Emerging evidence on brain atrophy as a measure of disease progression and treatment effect***

Paul M. Matthews, OBE

**08:10 – 08:30**

### ***Debate: Failure to act when RRMS patients have active disease should be considered negligent***

*For:* Robert Brenner

*Against:* Gavin Giovannoni

**08:30 – 08:40**

### ***Open discussion***

All

**08:40 – 08:45**

### ***Summary and close***

Siddharthan Chandran

## Thursday 23rd May 2013

0715-0815	<b>Breakfast with the experts</b> Neuro-ophthalmology – Gordon Plant, Luke Bennetto, Richard Metcalfe	
0715-0815	<b>Breakfast Symposium – Allergan – Practical Workshop – demonstration of the PREEMPT paradigm using dummy head models</b>	
0830	<b>Teaching: Science 3</b> Chair and introduction - Neil Scolding, Bristol Neurodegeneration, stem cells and brain repair – Siddharthan Chandran, Edinburgh Do stem cells have anything to offer for Parkinson's disease? - Roger Barker, Cambridge Stem cells in stroke - Keith Muir, Glasgow	
1000	<b>Coffee &amp; Exhibition</b>	
1030	Parallel sessions	<b>BNSU session – posters/platforms</b>
1200-1315	<b>Lunch &amp; Exhibition</b> <b>Lunchtime Symposium – Biogen Idec – No healthcare without Pharma</b>	
1315	<b>MS</b> – John Zajicek Derriford	<b>Epilepsy/neuroimmunology</b> – Yvonne Hart Newcastle, Michael Zandi Cambridge
1430	<b>ABN 2013 Medallist David Chadwick</b> 'Changing with the times' Chair – Martin Rossor Citation – Phil Smith	
1530	<b>Coffee &amp; Exhibition</b>	
1600	AGM & ABNT Forum	
1700	<b>Movement and functional disorder video session</b> Kailash Bhatia, Mark Hallett, Jon Stone, Mark Edwards	
1900 for 2000	<b>Gala Dinner – Kelvingrove Museum</b>	

## Friday 24th May 2013

0730-0830	<b>Breakfast Symposium – Teva UK – Debate 'Does progressive disease start on day 1?'</b>	
0900	<b>Case presentation competition, sponsored by ACNR</b> - Philip Smith, Cardiff	
1015	<b>Presidential Lecture</b> Geraint Fuller	
1100	<b>Coffee &amp; Exhibition</b>	
1130	<b>Teaching: Science 4</b> Dementia Clinical assessment of dementia – Chris Butler, Oxford Genetic testing and counselling for dementia – Huw Morris, Cardiff Clinical videos – Nick Fox, London	
1300	<b>Lunch</b>	
1415	<b>Teaching: Science 5</b> Update session Main developments in: Epilepsy – Sanjay Sisodiya, London MS – Neil Robertson, Cardiff Neuro-genetics – Nick Wood, London Peripheral nerve disease – James Overell, Glasgow	
1545	<b>CPC - Peter Enevoldson, Liverpool</b> Discussant – John Paul Leach, Glasgow	
1630	<b>Prize giving and close of meeting</b>	

# DOES PROGRESSIVE MS START ON DAY 1?

Association of British Neurologists Annual Meeting  
The Scottish Exhibition and Conference Centre (SECC), Glasgow  
Breakfast Satellite Symposium, Alsh Room

**Friday 24th May 2013 07:30 – 08:45**

## Agenda

### THIS HOUSE BELIEVES THAT PROGRESSIVE MS STARTS ON DAY 1

**07:30 Breakfast**

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**07:45 Welcome and introduction**

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**07:55 For the motion -**

Dr James Overell, Institute of Neurological Sciences, Glasgow

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**08:10 Against the motion -**

Dr Belinda Weller, Western General Hospital, Edinburgh

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**08:25 Debaters' response**

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**08:35 Discussion and Q&A**

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This session has been approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 1 category 1 (external) CPD credit.

This satellite symposium is sponsored by



Date of preparation: April 2013 UK/CNS/13/0006f



MS endeavour is an educational programme initiated and sponsored by Teva UK Limited

# Preparing for Neurology ST3 interviews



## Dr Marianne Novak

is a Neurology registrar, training in London and writing up her PhD on early brain changes in Huntington's disease. She is also the current ABNT BMA liaison representative.



## Dr Rumana Chowdhury

is a neurology trainee (ST5) at Kings College Hospital, London. She recently completed a PhD investigating learning and memory in ageing at the Institute of Cognitive Neuroscience (UCL). She was the ABNT Training and Education Representative from 2008-2012.

Most readers of ACNR are beyond the point of applying for speciality training positions themselves, but many will be asked for advice on the subject by junior colleagues. In this article, we give some tips about how to approach a Neurology ST3 interview, with the aim of helping both those applying for specialty training posts and those advising them. Please do consider passing this article on to any SHOs you know who are thinking about applying for a Neurology ST3 post. It will also be available online at [www.acnr.co.uk](http://www.acnr.co.uk)

### General points

The interview will generally constitute several stations, each with different interviewers and focusing on different topics. The precise format often changes from year to year so it is worth trying to find out as much as possible beforehand. Look at websites such as those from the RCP (<http://www.st3recruitment.org.uk>), the JRCPTB (<http://www.jrcptb.org.uk/Careers> and [Recruitment/Pages/Howtoprepareforinterview.aspx](http://www.jrcptb.org.uk/Recruitment/Pages/Howtoprepareforinterview.aspx)) and the local deaneries (various), and talk to colleagues who have recently been through the same process. The ABN website also contains a number of useful links (<http://www.theabn.org>). Remember to check beforehand which documents you need to bring along with you on the day (e.g. evidence of competencies, references). Try to have a mock interview and ask your friends to fire some questions at you: on the day, you need to show that you have put time and effort into preparing for your interview.

Some or all of the following topics are likely to arise:

### Personal experience and commitment to Neurology

Be ready to give a quick summary of your Neurology experience, and of where you see yourself in ten years' time. Be able to tell the interviewers succinctly why you want to be a Neurologist.

### Good Medical Practice

You should be familiar with this. It helps to try to frame as many of your answers as possible in terms of it. The GMC website contains both the full document and explanatory guidance notes ([http://www.gmc-uk.org/guidance/news\\_consultation/20477.asp](http://www.gmc-uk.org/guidance/news_consultation/20477.asp)).

### Clinical Governance

Know the six pillars of clinical governance (look at Wikipedia ([http://en.wikipedia.org/wiki/Clinical\\_governance](http://en.wikipedia.org/wiki/Clinical_governance)) if you're not sure). NHS Scotland (<http://www.clinicalgovernance.scot.nhs.uk/section1/definition.asp>) has additional information. There is a good chance that you will be asked about audit in depth (see below) but be prepared to know about/have evidence of the other pillars too.

### Audit

Make sure that you have a definition in mind (e.g. NICE's 'a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change') and be ready to discuss an audit you have carried out. Talk about it in terms of the audit cycle and make sure that you say either how the loop has been closed, or how it will be closed in the (near) future. Again, Wikipedia has a helpful entry ([http://en.wikipedia.org/wiki/Clinical\\_audit](http://en.wikipedia.org/wiki/Clinical_audit)); further details are available from NICE (<http://www.nice.org.uk/media/796/23/BestPracticeClinicalAudit.pdf>).

### Teaching

It helps if you've been on a formal course, but make sure you have some knowledge of different teaching styles and examples of when you have used them. Try to reflect beforehand on teaching as a two-way process and convey this in your answers.

### Clinical Scenarios

Don't panic if you're not sure about what is going on! The aim is to work through the differential process logically and demonstrate that you will be safe to work as a first year neurology registrar. Similarly, work through the basic steps even if you know the diagnosis immediately - demonstrate that you are safe. You can mention that you would discuss things with your senior if you are unsure. Examples of previous interview scenarios include foot drop, tongue fasciculation and transient global amnesia; talk to colleagues who have previous interview experience to find out more. The Practical Neurology Bare Essentials series (<http://pn.bmj.com>) is a brilliant resource for reading up on neurological conditions and MRCP clinical neurology case scenarios are

good practice for working through cases (we are not aware of any specific ST3 interview case scenario banks). Breaking bad news sometimes arises - always remember to put the patient first.

### Teamwork & leadership

Think about your experiences of both working in and leading teams and have some examples ready. The GMC website is helpful here ([http://www.gmc-uk.org/guidance/ethical\\_guidance/management\\_for\\_doctors.asp](http://www.gmc-uk.org/guidance/ethical_guidance/management_for_doctors.asp)). Be able to discuss your experience of working in a multidisciplinary team.

### Current issues/ hot topics

It is worth being aware of current healthcare issues such as changes to the NHS, revalidation, the Francis Report etc and be ready to discuss them. The BMA website is a good place to find information about this (<http://bma.org.uk>). You might also be asked about 'hot topics' in neurology such as stroke, dementia, and the provision of acute neurology services.

### Evidence-based medicine

Obviously you are unlikely to know every up-to-date development in Neurology, but try to have read a couple of recent papers and be able to summarise the main findings: you need to be able to show that you are able to practise evidence-based medicine. Have a look at the NICE summary guidelines for common neurological conditions (<http://www.nice.org.uk>). Consider signing up to free Neurology watch emails (e.g. [https://secure.jwatch.org/ecom/common/free\\_email\\_alerts.aspx?q=specialty\\_lp\\_signup](https://secure.jwatch.org/ecom/common/free_email_alerts.aspx?q=specialty_lp_signup)) to keep up to date with relevant research via regular alerts. Some previous interviews have included a request (with several weeks' notice prior to the interview) to prepare a short presentation on a recent research finding of the interviewee's choice.

### Final tips

Practice, practice, practice! Remember, the interview is your opportunity to show the panel that you are the kind of doctor that they want to work with in the future: show that you are professional, nice to patients, and - above all - safe. Good luck! ♦



# Should advanced therapies be started earlier in the treatment of Parkinson's disease?

**Highlights of a debate held at the World Congress on Controversies in Neurology (CONy), 12 April 2013, Istanbul, Turkey**

## Key points

- Debate confirms view that advanced treatments are currently started too late in Parkinson's disease
- Advanced treatments are effective if started when patients are refractory to optimal oral treatment and/or at the start of unpredictable response fluctuations
- Treatment should not be guided by chronological age
- Advanced treatments are effective in younger patients given earlier in the disease course

In deciding when to start advanced therapies in Parkinson's disease (PD), the question arises as to how the advanced stage of the disease is defined. The traditionally held view is that so-called advanced treatments – continuous subcutaneous apomorphine infusion, levodopa/carbidopa intestinal gel (LCIG) and deep brain stimulation – should be used at the end of the advanced stage of PD and not before. However opinions now differ as to when the advanced stage of PD starts and whether these advanced treatments could be effective if introduced much earlier, at the point where patients start to deteriorate despite optimal oral treatment and/or at the start of unpredictable response-fluctuations.

The spectrum of PD covers a potential 40-year span. Professor Okan Dogu, (Mersin University School of Medicine, Turkey) outlined that there is a premotor phase, where precursor symptoms such as hyposmia, constipation and REM sleep changes indicate the onset of neurodegeneration. These symptoms can occur 5–10 years before motor complications become evident and PD is actually diagnosed. Advanced PD is characterised by motor complications refractory to oral treatment, as well as non-motor symptoms. Advanced PD is not late-stage Parkinson's disease, however, when symptoms are refractory to all conventional therapies.

Professor Dogu conceded that motor fluctuations and dyskinesia are poorly controlled by current oral medications and continuous delivery of dopaminergic drugs using non-oral therapy or deep brain stimulation (DBS) should be used whenever motor and non-motor complications fail to respond to conventional oral therapy. However for Dr Teus van Laar (Groningen University Medical Center, The Netherlands) advanced PD treatments are currently started too late (and sometimes neglected altogether), with a clear impact on social function and activities of daily living. In his view, the timing of these therapies is crucial, because the therapeutic window narrows as PD progresses.

Dr van Laar believes advanced PD is defined by the occurrence of unpredictable on-off fluctuations and/or severe hyperkinesia not responsive to oral treatment. Most patients show these symptoms within 10 years of diagnosis. However, he noted that in The Netherlands there are 45,000 patients with PD and one-third

of these will have unpredictable random fluctuations, around 10% of which are really troublesome (i.e. 1500 patients), yet figures show that only 10% of these 1500 patients are receiving adequate therapy, indicating undertreatment.

If advanced treatments are started too late in the course of PD, the clinical outcome is not as positive as it might be with earlier use. Inclusion data from several studies on LCIG and continuous apomorphine infusion show that patients are included in these studies 7–8 years after the start of unpredictable fluctuations, with a huge impact on quality of life<sup>1,2</sup>. Dr van Laar also presented data from the recent EARLY STIM trial<sup>3</sup> supporting this hypothesis, showing that early DBS offers benefits in terms of patient-rated measures of quality of life and motor function, even in patients already receiving best medical treatment. For Dr van Laar, the message from this study is that if advanced treatments are started while there is still room for improvement then there is longer-lasting benefit. This means treating younger patients earlier in the course of their disease.

However, while Professor Dogu conceded that all three advanced therapies are powerful strategies for advanced PD, in his view their side effects, invasiveness and cost limit their use in clinical practice. Also important is the sustainability of both continuous apomorphine infusion and LCIG, with drop-out rates on account of adverse effects. Patients should therefore be carefully selected for these treatments.

For Professor Murat Emre (Istanbul University, Turkey), who summed up the debate, treatment decisions depend on patient, environment and context. For example, a PD patient still of working age living in a complex social environment may need advanced treatment earlier than an older, less active patient. For this reason, chronological age is not the best guide when considering advanced treatment.

## Conclusion

**Having listened to the debate, the audience in Istanbul were evidently convinced by Dr van Laar's argument. Voting was overwhelmingly in favour of starting advanced therapies earlier in the course of PD than is currently accepted practice. Further empirical data is required from clinical studies to confirm the compelling evidence that already exists from clinical experience.**

## References

1. Garcia Ruiz PJ, Sesar Ignacio A, Ares Pensado B et al. *Mov Disord* 2008; 23(8): 1130-6.
2. Fasano A, Ricciardi L, Lena F et al *Eur Rev Med Pharmacol Sci* 2012; 16(1): 79-89.
3. Schuepbach WM, Rau J, Knudsen K et al. *N Engl J Med* 2013; 368: 610-22.

*Prescribing information can be found overleaf*

**This article was commissioned by Britannia Pharmaceuticals Ltd and was written by Helen Lawn & Associates. The debate was part of the Britannia sponsored CME accredited plenary session on Parkinson's disease - held on 12 April during the recent CONy Congress in Istanbul.**

**Britannia**  
Pharmaceuticals Ltd

**PRESCRIBING INFORMATION**

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. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. 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 bases; 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 because of the risk of postural hypotension, 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 bronchospasm.

**Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitis. 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 lightheadiness 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*

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**Muddied waters (on the brain)**

Diagnosis in the dementias remains challenging. The prospect of disease modifying treatments for neurodegenerative pathologies demands an improvement in the prediction of underlying pathology during lifetime. There is an argument that diagnostic accuracy is better in PSP than other diseases. The NNIPPS study found those with a clinical diagnosis of PSP were likely to have tau-based PSP pathology in 95% of cases (Bensimon et al). However, uncertainty remains around patients with PSP pathology at post-mortem who may have a lifetime diagnosis of other conditions such as Parkinson's disease, or no diagnosis at all. The waters are further muddied by a study from the Queen Square group (Magdalinou et al) who identified three patients with a lifetime diagnosis of idiopathic Normal Pressure Hydrocephalus (iNPH), but tau-associated PSP pathology at post-mortem, and an additional patient with clinical iNPH and alpha-synuclein Parkinson's disease pathology. All four patients had an initial positive response to lumbar puncture, classically considered to be central to a diagnosis of iNPH alongside the triad of urinary incontinence, impaired balance and cognitive decline. One may wish to quibble that some red flags were present during life, such as the presence of swallowing problems in 3/4 patients, classic MRI findings of mid-brain atrophy in one patient, and sufficient concern about a co-existing diagnosis in two patients not to proceed with shunting. However, eye movements were not noticed to be abnormal until late in the disease course in all three subjects and the fact remains that the primary clinical label during life was iNPH in all four patients. The authors accept their sample may be biased by the high number of patients with movement disorders in their brain bank. Previous reports have raised more issues concerning vascular disease or Alzheimer's pathology in the context of clinical iNPH. However, a single subject with PSP was identified in a series from the Mayo Clinic (Klassen et al). We are not told when the diagnoses were made, and recent attempts to strengthen diagnostic guidelines for both iNPH and PSP may assist the clinician. Despite this, predicting neurodegenerative pathology during life remains challenging and a diagnosis of iNPH should be made with caution and an open mind, even if there is an initial response to lumbar puncture. – **TR**

**Magdalinou NK, Ling H, Smith JDS, et al.**

**Normal pressure hydrocephalus or progressive supranuclear palsy? A clinicopathological case series.**

**Journal Of Neurology 2013;260:1009-13.**

**Bensimon G, Ludolph A, Agid Y, et al.**

**Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. Brain 2009;132:156-71.**

**Klassen BT, Ahlskog JE. Normal pressure hydrocephalus: how often does the diagnosis hold water? Neurology 2011;77:1119-25.**

**Brain pathology goes 3D**

While Drosophila biologists have long been able to produce beautiful, technicolour images of whole mount preparations, mammalian neuroscience has been left behind in the 2D world. Wouldn't it be amazing if we could do human brain pathology in 3D? Researchers from Stanford University pushed the boundaries of tissue fixation and appear to have developed a method, termed CLARITY, which makes brain tissues 'optically and chemically accessible'. The Deisseroth lab at Stanford first fixed and stabilised cellular proteins, nucleic acids and other molecules (but, importantly, not lipids) using conventional fixatives, together with hydrogels such as acrylamide. They then used a detergent to wash away the unfixed lipids, accelerating this process using electrophoresis. The result is 'clarified' tissue, free of the optical dispersion caused by lipid membranes, and more permeable to antibodies for

immunoprofiling. Their images are simply stunning. The 'invisible brain' is truly astounding!

Their pictures and 3D fly-through videos clearly indicate the power of this tool. The ability to resolve subcellular architecture in 3D, repeatedly antibody stain and not have to section are attractive, and although it may take weeks to process a whole mouse brain, this may be a small price to pay for the sheer quality and quantity of data one could obtain. Aside from pretty mouse brains, CLARITY is also applicable to other vertebrates, most importantly humans. Archived brain specimens can be clarified.

The group provide detailed directions for setting up the apparatus needed to 'clarify' tissue. One just hopes that other research labs and brain banks will be able to easily use their methods to replicate and even improve upon their results. – JS

**Chung K, Wallace J, Kim SY, et al.**

**Structural and molecular interrogation of intact biological systems.**

*Nature*. 2013 Apr 10. doi: 10.1038/nature12107

## NMDAR encephalitis – hit hard and fast?

Most clinicians will remember their first patient with Anti-NMDAR encephalitis. First described in 2005, as a paraneoplastic, neuropsychiatric disorder associated with ovarian teratoma, Dalmau and colleagues first identified the specific antibody associated with this syndrome in 2007. Patients with anti-NMDAR encephalitis typically develop a multistage illness that encompasses psychosis, seizures, abnormal movements, reduced levels of consciousness and autonomic instability.

In the largest observational study of patients with anti-NMDAR encephalitis published to date, Titulaer and colleagues recently described in the *Lancet Neurology* the presentation, treatment and outcome factors of 577 patients with the disease (median age 21 years, range 8 months to 85 years). Of this cohort, most (501) had at least four months follow-up, with a median follow-up time of two years. Whilst seizures or movement disorders were the most frequent presenting symptoms in children, adults more commonly presented with behavioural disturbance. In total, 38% of patients had an underlying malignancy, which were nearly all ovarian teratomas. Non-teratoma neoplasms accounted for only 4% of tumours. As awareness of this disorder among clinicians has increased, people with atypical presentations are increasingly being tested for antibodies. Interestingly, only 1% of patients in this cohort remained monosymptomatic at four weeks suggesting that antibody testing in such patients is unlikely to yield positive results.

In early studies, response to tumour removal and first-line immunotherapies (steroids, intravenous immunoglobulins and plasmapheresis) was sub-optimal in many patients but there has been controversy surrounding the benefits of

escalating to second-line immunotherapies (rituximab and/or cyclophosphamide). Of the 472 patients in this cohort treated with tumour removal and/or first-line therapies, 53% had improved symptomatically within four weeks. Of the remaining 47% of "non-responders", just over half were prescribed second-line treatments. Results supported the theory that those patients receiving additional treatment with rituximab and/or cyclophosphamide had better outcomes than patients who only received first-line therapies, with 78% of treated patients attaining a modified Rankin Scale score of 0-2 by 24 months compared with only 55% those who did not receive second-line immunotherapies. Furthermore, those initial "non-responders" treated with second-line immunotherapies had a comparatively reduced number of relapses and minimal adverse events were reported.

Overall this study has provided important information about the presentation, treatment and prognosis of this serious but treatable autoimmune disease. It provides evidence that early intervention results in better outcomes and should encourage clinicians to intervene with cyclophosphamide and/or rituximab if first line therapies fail to lead to a significant improvement after four weeks of treatment. Although limited by not being randomised, this study sets the stage for future trials to establish the efficacy of each individual treatment as well as recommended duration of therapies. – GC

**Titulaer MJ et al.**

**Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study.**

*Lancet Neurol*. 2013 Feb;12(2):157-65

## Caspr2 and limbic encephalitis

The classical phenotype of anti-voltage gated potassium channel (VGKC) antibody limbic encephalitis (LE), in which patients present with psychiatric deterioration, encephalopathy and seizures, is now well recognised. However, recent work has identified that the antibody target in autoimmune LE is not the VGKC itself but rather VGKC associated proteins that co-precipitate in the radioimmunological assay (RIA). The contactin-associated protein-2 (Caspr2), which forms part of the molecular scaffold responsible for maintaining VGKC appears to be one such antibody target. Balint and colleagues from Heidelberg have published a case of Caspr2 antibody positive but VGKC antibody negative LE. They detected the antibody (IgM; titre 1:100) with a cell-based assay using full length human Caspr2 (Euroimmun) after standard RIA using brain tissue extract was negative. Their case is noteworthy as, in addition to the usual features of the disease, the patient manifested cerebellar ataxia, myoclonus and dyskinesia suggesting that Caspr2 antibody positive LE may have a broad and severe clinical phenotype. The authors argue that more targeted assays should be employed for detecting antibodies

in LE. Over the coming years, distinguishing the different clinical subtypes of autoimmune LE will be increasingly relevant in helping to guide prognosis and therapy. – TH

**Balint B, Regula JU, Jarius S, Wildemann B.**

**Caspr2 antibodies in limbic encephalitis with cerebellar ataxia, dyskinesias and myoclonus.**

*J Neurol Sci*. 2013 Apr 15;327(1-2):73-4.

doi: 10.1016/j.jns.2013.01.040. Epub 2013 Mar 5.

## Seeing music

In some recent pieces on the neurology of music, Oliver Sacks summarises 8 case histories of subjects, including 2 with Parkinson's disease, with visual hallucinations consisting of the staves and notes of musical notation, which on closer inspection tend to reveal nonsensical 'pseudomusic', a feature those with text hallucinations also experience. He contrasts this to musical alexia without print alexia, as described in a personal account by Ian McDonald. Zamm and colleagues apply diffusion tractography to colour-music synesthesia and controls and provide some evidence for the role of the white matter bundle of the inferior fronto-occipital fasciculus (IFOF) as substrate for this form of synesthesia (having previously highlighted the left superior temporal gyrus in subjects with perfect pitch). Basaglia-Pappas and colleagues design a musical battery of old French songs (the POP 10), revealing a strong reminiscence stimulating effect of the test which could be harnessed in occupational and cognitive therapy. – MZ

**Sacks O. Hallucinations of musical notation. *Brain*. 2013 Mar 25 [advanced access]**

**McDonald I. Musical alexia with recovery: a personal account. *Brain* 2006;129:2554-61.**

**Zamm A, Schlaug G, Eagleman DM, Loui P. Pathways to seeing music: Enhanced structural connectivity in colored-music synesthesia. *Neuroimage*. 2013 Jul 1;74:359-66.**

**Loui P, Zamm A, Schlaug G. Enhanced functional networks in absolute pitch. *Neuroimage*. 2012 Nov 1;63(2):632-40.**

**Basaglia-Pappas S, et al. Exploration of verbal and non-verbal semantic knowledge and autobiographical memories starting from popular songs in Alzheimer's disease. *Int Psychogeriatr*. 2013 May;25(5):785-95.**

### Panel of reviewers

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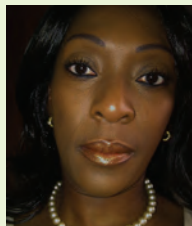
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# Epilepsy in the Elderly



## Erica B Chisanga,

*Msc Epileptology, MPH, BSc Nursing*  
has been a Consultant Nurse in epilepsy at Cambridge University Hospitals since 2010. An ILAE Gower Prize winner in 2006 and Independent non-medical prescriber, Ms Chisanga manages patients with epilepsy from young adulthood, including pregnant women and those with a learning disability. She has been invited to lecture at national scientific meetings and publishes in healthcare journals.

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The steady growth in the number of people over the age of 65 in industrialised countries is estimated to reach around 30% by 2030, doubling since 1985 (Figure 1). Consequently, we shall see a considerable rise in the number of elderly people with epilepsy most of whom, unlike younger patients, have multiple comorbidities. The complexity of this situation will not only impact health and social resources but also present challenges in managing the condition. This article will focus on the specific needs of the elderly which present unique challenges. These include diagnostic problems, complexities of treatment and social impact on an already vulnerable population.

The trend in the population over the age of 65 years and over in the UK, showed an increase from 15% in 1985 to 17% in 2010, that is an increase of 1.7 million people.<sup>1</sup> Projections by the Office of National Statistics for this population group suggest they will account for 23% of the total population as illustrated in Figure 1.

The fastest growth in this group is more evident in those who are 85 and above, i.e. 0.7 million in 1985 doubling to 1.4 million and 3.5 million in 2010 and 2035 respectively, thereby accounting for 5% of the total population of the UK.<sup>1</sup> Following a number of epidemiological studies undertaken in industrialised countries, the pattern of incidence of epilepsy has been shown to have a bi-modal distribution with the first peak in the first few years of life and the second and more striking peak after age 60.<sup>2,5</sup> Incidence rates in the elderly of over 100 per 100,000 have been reported.<sup>6,7</sup>

The prevalence of epilepsy also increases with advancing age but to a lesser degree. Fatalities often result in those presenting with status epilepticus in acute symptomatic epilepsies.

Several studies show variability in aetiology and risk factors.<sup>6,8</sup> These include cerebrovascular disease, neoplasms, metabolic and toxic causes, head injuries, infection, subdural haematoma, non-vascular dementias etc. Stroke however has been found to be a definite risk factor responsible for a high proportion of cases,<sup>2</sup> with clinically unsuspected cerebral infarcts often demonstrated on CT scans of elderly patients with epilepsy.<sup>9</sup> Moreover, late onset seizures carry nearly a threefold risk of subsequent stroke, when compared to age-matched controls<sup>10</sup>, a greater risk than hypercholesterolaemia or smoking, which means that the onset of seizures in this age group also necessitates the management of vascular risk factors. Seizures often have more than one cause i.e. an acute cerebral insult such as hyperglycaemia may trigger epileptic activity in pre-existing injury.

## Types of epilepsy

Focal epilepsies are more commonly seen than generalised types in the elderly.<sup>6</sup> The common epileptic syndromes in the elderly are:

- Remote symptomatic seizures e.g. due to preceding stroke.
- Acute symptomatic or provoked seizures e.g. due to acute stroke, metabolic disturbance or trauma.
- Symptomatic seizures due to progressive disease such as tumour or dementia.
- Cryptogenic i.e. unidentifiable cause but presumed to be symptomatic.

## Diagnostic challenges

The diagnosis of epilepsy is clinical. In the elderly however, it may be difficult to differentiate seizures from possible underlying medical problems such as hypoglycaemia, syncope,

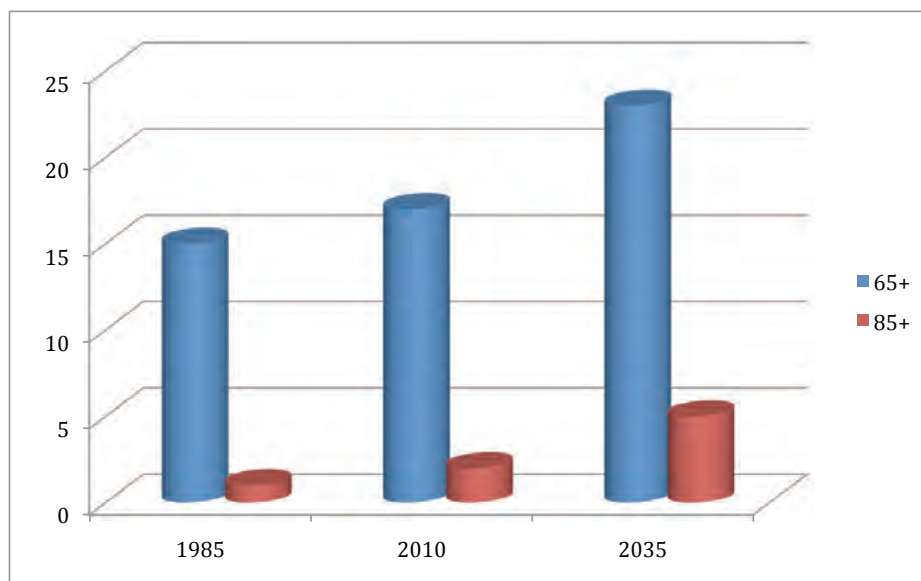


Figure 1: Source: Office for National Statistics, National Records of Scotland, Northern Ireland Statistics and Research Agency [1985 to 2010 Mid-year estimates, ONS, NRS, NISRA; 2011 to 2035 National Population Projections, (2010-based), ONS].

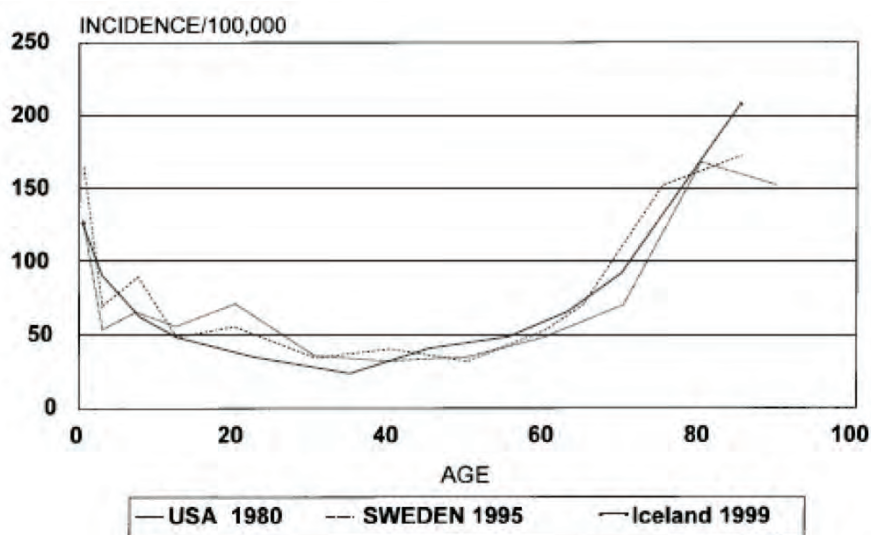


Figure 2: Source: Banerjee & Hauser (2007)<sup>20</sup>

confusional states etc. Another compounding problem is the lack of obtaining a reliable witness account of events especially where the elderly person lives alone or lives with a spouse with impaired memory. This may lead to misdiagnosis. For example, focal seizures are often misdiagnosed as transient cerebral ischaemic attacks, where the stereotypical epileptic symptoms have not been recognised.<sup>2</sup> Epileptic seizures in the elderly tend to be associated with prolonged post-ictal states.<sup>11</sup> For example, a prolonged Todd's paresis is frequently misdiagnosed as a stroke. Epilepsia partialis continua may be misdiagnosed as a movement disorder.<sup>2</sup> Conversely, carotid stenosis may cause transient ischaemic attacks, manifesting with recurrent focal motor activity of one arm which may be diagnosed as epilepsy. Generalised epilepsies do occasionally first present in old age,<sup>12</sup> especially as non-convulsive status epilepticus and patients who present with none of the usual infective or metabolic causes of confusion should be screened early with EEG; a challenge in some hospitals. Studies suggest that the diagnosis of this treatable condition is generally delayed at least several days.

### Prognosis

The risk of seizure recurrence in persons over the age of 60 was reported to be at 80% at 52 weeks with remote symptomatic seizures carrying an 85% risk at 36 months.<sup>13</sup> An extended follow-up study reported that presence of Todd's paresis or previous acute symptomatic seizures relating to the initial insult appeared to elevate recurrence risk.<sup>14</sup>

### Treatment

There is paucity of data to allow for rational therapeutic policies to be made for treatment of seizures and epilepsy in the elderly. A retrospective study showed that of the patients not treated and followed up for a year, 62% remained seizure free and 26% had less than three seizures per year.<sup>15</sup> There are no controlled clinical studies available. Such information is necessary to make a case for treatment against epilepsy and its complications. The studies available however, report that low dose antiepileptic medication achieves seizure freedom in a majority of older people. The proportion of patients who achieved seizure freedom in a veterans' trial of antiepileptic drug treatment in adults was higher in the older than the younger patients.<sup>16</sup>

There is also the question of what antiepileptic medication to use. The high rate of co-morbidities, accompanying co-medication and susceptibility to side effects as well as the ageing brain, suggest elderly patients may require very specific consideration with regard to choice of treatment. To add to the question of whether to treat or not is the consideration of aetiology which also forms the basis for counselling the patients and carers, a role that specialist nurses contribute to significantly. Acute symptomatic seizures are most effectively controlled by treating the underlying cause e.g. treatment of infection.

The choice of anti-epileptic drug (AED) for recurrent unprovoked seizures is an area where the few clinical trials have not kept up with changes in common practice. Certain principles can be applied. Pharmacokinetic considerations may influence drug choice or

dose, especially renal or hepatic function, which are commonly altered in the elderly. Pharmacokinetic interactions, for example of enzyme inducing AED on warfarin, may determine choice and in the veterans' study, the mean number of other drugs being taken was five. Pharmacodynamic interactions are also common, particularly hyponatraemia when carbamazepine or oxcarbazepine is combined with a thiazide diuretic and this combination should be avoided.

Commonly used AED in the elderly include carbamazepine, lamotrigine, levetiracetam and sodium valproate.<sup>2</sup> Phenytoin was also found to be a useful first line but had more treatment failures when compared to sodium valproate in a multicentre trial, due to poor control and adverse effects.<sup>17</sup> In spite of this, phenytoin is still used as first line by many physicians in departments of medicine for the elderly given its low cost, accessibility and ease of administration i.e. once daily dosing.<sup>18</sup> The disadvantage of its linear kinetics makes small dose adjustments produce plasma concentrations associated with toxicity or inefficacy, which far outweigh its advantages. Lamotrigine is useful and generally well tolerated. It has a potential to cause idiosyncratic reactions. In the elderly group it may also cause insomnia and tremor. It is the only new drug where clinical trials have been conducted in the elderly (against carbamazepine) providing an evidence base, favouring its use.<sup>19</sup> Levetiracetam's lack of drug interactions and generally good tolerability and potentially rapid dose titration makes it widely used in the elderly although there are no specific comparative trials to support its use. Carbamazepine's sedative effects may limit tolerability but this can be managed with a low once or twice daily starting regimen increased slowly. There is a small incidence of bone marrow suppression and hepatitis which however may be increased by age. Its antidiuretic hormone-like effect may produce fluid retention and precipitate cardiac failure in the elderly. It may also precipitate abnormal cardiac conduction in elderly patients with pre-existing cardiac disease. Sodium valproate, a non-hepatic inducing drug, is useful in the elderly who may also be receiving concomitant treatment thus would not reduce their efficacy. Its limiting adverse effects include sedation, tremor, Parkinsonism, cognitive slowing and gastrointestinal disturbances. Our preference is for lamotrigine or levetiracetam as first line in this age group.

### Social isolation

A diagnosis of epilepsy may cause social isolation in most people, more so the elderly who may be living alone or living with another

*The burden of epilepsy in the elderly will increase with the growth of the ageing population*

elderly physically or mentally frail spouse. The fear of falling during an epileptic seizure may cause them to confine their mobility to the household. Driving restrictions may particularly affect the elderly with comorbidities affecting their mobility. Epilepsy specialist nurses can help to minimise this level of isolation by collaboratively working with the general practitioners, community matrons, occupational therapists, family and carers. In addition to the counselling specialist nurses provide to the elderly, they can also facilitate access to day centres and safe means of transportation so that patients do not remain confined to their homes.

### Conclusion

The burden of epilepsy in the elderly will increase with the growth of the ageing population. Its diagnosis in this age group requires consistent enquiry over and above the scanty information which may be presented by the elderly person. In selected cases, prevaricating over treatment should be seen as a cautious and safe management and families can be reassured that it is not due to indecisiveness. Once the correct diagnosis has been made, the condition is easier to bring under control than in young adults. Although evidence is limited, newer drugs should generally be considered early, because of better adverse effect and pharmacokinetic profiles. Management should include an epilepsy specialist nurse for this particularly vulnerable patient group. ♦

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### BOOK REVIEW

## Fast Facts: Epilepsy (5th edition)

That *Fast Facts: Epilepsy* is in its fifth edition provides a more eloquent recommendation than any personal comments of mine.

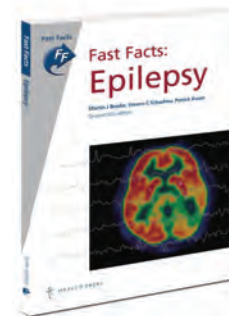
In accordance with the principles of the Fast Facts series, it aims to provide a brief overview and an accessible point of reference. Its 100 or so A5 pages are divided into chapters covering such topics as 'classification of seizures and syndromes', 'general principles of pharmacological management', 'individual antiepileptic drugs' and 'non-pharmacological management'. There are numerous useful tables (including 'key points' for each chapter), several illustrations, comprehensive glossary, indexing and references and contact details for organisations that aim to support patients with epilepsy and clinicians managing the condition (within the UK and internationally).

Niggle criticisms would include the slight distraction for the British reader of American spellings. The glossary defines 'ictal' as 'relating to, or caused by a seizure'. This is perfectly true for the text to which the glossary applies; however, I would have preferred for it to be acknowledged that the term can be applied to any type of neurological

attack. The chapter on individual drugs was the one I found most useful but it was not as explicit as I would have liked in stating how rarely some of the drugs are used as anticonvulsants (e.g. Vigabatrin, Felbamate and even Gabapentin). As you might expect, the chapter on diagnosis was the one that I found duller, but it would have been inappropriate in a volume of this size to include the rare and fascinating.

Though brief, the chapters on 'epilepsy in specific populations', 'quality of life issues' and 'future trends' enrich the volume. Though I am sure that all epilepsy facts that can be learned 'fast' should already be within the grasp of a Consultant Neurologist, I was pleased to read about the use of the morning after pill in those taking anticonvulsants and about which herbal remedies might worsen seizures.

Finding fault with this book was more difficult than reading it. It is very easy to recommend to busy trainees about to start working in the epilepsy clinic. For the typical Neurologist it might have value as a quick reminder of the merits and demerits of less familiar modern antiepileptic drugs. ♦



**Editors:** Martin Brodie, Steven Schachter, Patrick Kwan  
**Published by:** Health Press Limited, Oxford Press, 2012  
**Price:** £15.00  
**ISBN:** 978-1-908541-12-3

**Reviewed by:** Rhys Davies, The Walton Centre, Liverpool, UK.

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**Tapclob 5mg/5ml and 10mg/5ml Oral Suspension may not be directly equivalent to other clobazam products at the same strengths of 5 mg or 10 mg (either tablets or extemporaneously prepared formulations). Once titrated to an effective dose, patients should remain on their treatment and care should be taken when initiating treatment or switching between clobazam products. Please refer to Summary of Product Characteristics when prescribing.**

#### Prescribing Information for Tapclob 5mg/5ml and 10mg/5ml Oral Suspension

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**Presentation:** An off white viscous suspension with a raspberry odour. **Indications:** Clobazam is indicated for the short-term relief (2-4 weeks) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short term psychosomatic, organic or psychotic illness. It should not be used to treat short-term "mild" anxiety. Before treatment of anxiety states associated with emotional instability, it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment. Indeed, in patients with anxiety associated with depression, clobazam must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepine (such as clobazam) alone, can precipitate suicide in such patients. In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for adjunctive, i.e. not for primary treatment. Clobazam may be used as adjunctive therapy in epilepsy. **Dosage and Administration: For oral use only. Once titrated to an effective dose of clobazam, patients should remain on their treatment and care should be exercised when changing between different formulations. Adults and adolescents over 15 years of age: Treatment of Anxiety:** 20-30mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in the treatment of adult in-patients with severe anxiety. The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced. It should not be used for longer than 4 weeks. If extension beyond the maximum treatment period is necessary, treatment must not be extended without re-evaluation of the patient's status. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. **Treatment of epilepsy in association with one or more other anticonvulsants:** Starting dose of 20-30 mg/day, increasing as necessary up to a maximum of 60 mg daily. The patient must be re-assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment. Treatment should always be withdrawn gradually. **Elderly:** Doses of 10-20 mg daily in anxiety. Treatment requires low initial doses and gradual dose increments under careful observation. **Paediatric population:** Start with low initial doses e.g. 5mg daily and gradual dose increments under careful observation. A maintenance dose of 0.3 to 1mg/kg body weight daily is usually sufficient. No dosage recommendations can be made in children under 6 years of age. **Contra-Indications:** Patients with hypersensitivity to benzodiazepines or any of the excipients of clobazam; patients with any history of drug or alcohol dependence; patients with myasthenia gravis; patients with severe respiratory insufficiency; patients with sleep apnoea syndrome; patients with severe hepatic insufficiencies. During the first trimester of pregnancy and in breast-feeding women. Clobazam must not be used in children between the ages of 6 months and 3 years, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication. **Warnings And Precautions:** Use with extreme caution in patients with personality disorders. Use with caution in patients with myasthenia gravis, spinal or cerebellar ataxia or sleep apnoea; chronic or acute severe respiratory insufficiency; impaired renal or hepatic function; Reduce dose if necessary. Patients with a rare hereditary problems of fructose intolerance should not take this medicine. **Interactions:** Clobazam may interact with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics,

anticonvulsant drugs, anaesthetics and sedative antihistamines; lithium; alcohol; Carbamazepine, muscle relaxants, analgesics and nitrous oxide, narcotic analgesics. Drugs that inhibit the cytochrome P-450 enzyme (mono-oxygenase) system (eg cimetidine), Phenytoin and valproic acid - dosage of clobazam should be determined by monitoring the EEG and the plasma levels of the other drugs checked. **Fertility, Pregnancy And Lactation:** If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become pregnant or suspects that she is pregnant. If the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate such as hypothermia, hypotonia, moderate respiratory depression and difficulties in drinking "floppy infant syndrome", may occur and they may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. Benzodiazepines are found in the breast milk and should not be given to breast feeding mothers. **Effects on ability to drive and use machines:** Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. **Undesirable Effects:** Clobazam may cause sedation, leading to fatigue and sleepiness, especially at the beginning of treatment and when higher doses are used. Drowsiness, dizziness or dryness of the mouth, constipation, loss of appetite, nausea, or a fine tremor of the fingers have been reported. These are more likely to occur at the beginning of treatment and often disappear with continued treatment or a reduction in dose. Paradoxical reactions, such as restlessness, irritability, difficulty in sleeping, anxiety, delusion, nightmare, hallucinations or suicidal tendencies may occur, especially in elderly and in children. In the event of such reactions, treatment with clobazam must be discontinued. Anterograde amnesia may occur, especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour. Clobazam may cause respiratory depression, especially if administered in high doses. Isolated cases of skin reactions, such as rashes or urticaria, slowing of reaction time, ataxia, confusion and headaches. Disorders of articulation, unsteadiness of gait and other motor functions, visual disorders (e.g. double vision), weight gain, or loss of libido may occur, particularly with high doses or in long-term treatment. These reactions are reversible. Pre-existing depression may be unmasked during benzodiazepine use. Tolerance and physical and/or psychic dependence may develop, especially during prolonged use. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Abuse of benzodiazepines has been reported. When used as an adjuvant in the treatment of epilepsy, this preparation may in rare cases cause restlessness and muscle weakness. **Product Licence Number:** 5mg/5ml PL 00156/0322, 10mg/5ml PL 00156/0323. **Product Licence Holder:** Martindale Pharmaceuticals Ltd T/A Martindale Pharma, Bampton Road, Harold Hill, Essex RM3 8UG. **Basic NHS Price:** Tapclob 5mg/5ml Oral Suspension £130.97, Tapclob 10mg/5ml Oral Suspension £135.79. **Legal Category:** POM. **Date of Preparation:** January 2013. For more details contact: Martindale Pharma, Hubert Road, Brentwood, CM14 4JY, Tel: 01277 266600.

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Martindale Pharma Tel: 01277 266600, Fax 01708 382739, e-mail [drugssafety@martindalepharma.co.uk](mailto:drugssafety@martindalepharma.co.uk).

# Diagnosis and Management of Headaches: NICE CG150



## Professor Mark Baker,

Mark Baker is the Director of the Centre for Clinical Practice (CCP) and is responsible for designing and operating methods and systems to produce clinical guidelines for the NHS. These products integrate, where appropriate with those produced by the health technology evaluation and public health excellence centres, to form comprehensive prevention and treatment recommendations for practitioners in the NHS and the wider public health community. CCP is also responsible for the work of the Medicines and Prescribing Centre including summaries of evidence on new medicines and unlicensed and off-label medicines and the management of the contract for the BNF.

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Last year, the UK's National Institute for Health and Care Excellence (NICE) published its first clinical guideline for the National Health Service (NHS) on the diagnosis and management of headache in adults and young people.

The guideline advises on the care for the most common primary headaches – tension-type headache, migraine and cluster headache – as well as medication overuse, which has been estimated to affect 1-2% of the population.

NICE has issued its guideline to support clinicians, such as neurologists and general practitioners, in their clinical decision-making by outlining the assessment criteria, diagnostic tools and treatments, which are proven to be most clinically and cost effective. It is hoped that this will standardise care of headaches across the NHS so that people with the condition receive the best treatments and support possible, in a timely and coordinated manner.

### Key recommendations

This guideline recommends some drugs for indications for which they do not have UK marketing authorisations for (at the date of publication – September 2012), if there is good evidence to support their use in this way. To view NICE's full recommendations, details about off label use and evidence-base, download the clinical guideline from the NICE website.

### All headache disorders

- Do not refer people diagnosed with tension-type headache, migraine, cluster headache or medication overuse headache for neuroimaging solely for reassurance

### Information and support for people with headache disorders

- Include the following in discussions with the person with a headache disorder:
  - a positive diagnosis, including an explanation of the diagnosis and reassurance that other pathology has been excluded and
  - the options for management and
  - recognition that headache is a valid medical disorder that can have a significant impact on the person and their family or carers

### Migraine with or without aura

#### Acute treatment

- Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and parac-

etamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptan.

- For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:
  - offer a non-oral preparation of metoclopramide or prochlorperazine and
  - consider adding a non-oral NSAID or triptan if these have not been tried.

### Prophylactic treatment

- Offer topiramate or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception.

### Cluster headache

#### Acute treatment

- Offer oxygen and/or a subcutaneous or nasal triptan for the acute treatment of cluster headache.
- When using oxygen for the acute treatment of cluster headache:
  - use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag and
  - arrange provision of home and ambulatory oxygen.
- When using a subcutaneous or nasal triptan, ensure the person is offered an adequate supply of triptans calculated according to their history of cluster bouts, based on the manufacturer's maximum daily dose.

### Conclusion

The NICE clinical guideline offers practical evidence-based advice for nurses and other health-care professionals on how to diagnosis and manage headaches.

Implementation of the guideline will improve the assessment and management of headaches and enable patients to obtain appropriate treatment sooner.

To download the NICE clinical guideline and to access support tools or information to give to your patients, please visit: [www.nice.org.uk/CG150](http://www.nice.org.uk/CG150) ♦



# PREVIEW 3rd World Parkinson Congress World Parkinson Coalition Inc.



**Conference details:** 1 October, - 4 October 2013, Montreal, Canada.  
**Report by:** Elizabeth Pollard – Executive Director.

The third World Parkinson Congress, also known as the WPC 2013, will offer a unique experience for neuroscientists, clinical researchers, rehabilitation professionals, geriatricians, people with Parkinson's, caregivers, and policy makers. Under the leadership of Co-Chairs Drs Stanley Fahn and Jon Stoessl, more than 100 committee members from 19 countries have helped to shape the WPC 2013 and make it the most important meeting for people interested in Parkinson's disease.

The WPC 2013 will have nearly 3,500 delegates from more than 50 countries in attendance. Sessions will include large morning plenaries, medium sized lectures, interactive workshops and our new, very intimate "Meet the Expert Roundtables" which will allow for cross-pollination of delegates and better exchange of ideas.

The programme, under the guidance of Dr Serge Przedborski and his three co-chairs has been carefully put together over the past year by a dedicated team of 50 academics, clinicians and those who experience the reality of living with Parkinson's. Topics will highlight the most germane issues in Parkinson's today including gene and cellular therapy, neuroprotection, non-motor manifestations of Parkinson's, rehabilitation options, clinical trials, physical therapy, advocacy and care delivery to name a few. The provisional programme can be viewed at [www.worldpdcongress.org](http://www.worldpdcongress.org).

## Abstracts

Abstracts are being accepted on a wide range of scientific topics. In addition, we will have a special category for advocates and others to submit abstracts on programmes and projects that may not be scientific in nature but that are also changing the lives of people living with Parkinson's at the grass-roots level.

## Hot Topics

Twelve of the most outstanding abstracts will be presented each morning to a large audience just before the plenary sessions. This will let junior investigators take centre stage in front of some of the most influential neuroscientists and renowned

Parkinson's authorities.

The aim of WPC 2013 is to bring the world of Parkinson's together in one place to not only learn from each other in scientific sessions, poster tours, and other talks, but to build a community that is representative of everyone researching and touched by Parkinson's.

The cure for Parkinson's will ultimately be accelerated through working together as a team. Join the WPC team and be a part of the solution. ♦

**See you in Montreal in October.**



To list your event in this diary, email brief details to Rachael Hansford at [Rachael@acnr.co.uk](mailto:Rachael@acnr.co.uk) by 6th June, 2013

## May

**ABN Annual Meeting**  
21-24 May, 2013; Glasgow, UK  
[www.abn.org.uk](http://www.abn.org.uk),  
T. 020 7405 4060, E. [info@theabn.org](mailto:info@theabn.org)

**ABN Eisai Debate: When should an epilepsy patient be referred to an epilepsy specialist**  
22 May, 2013; Glasgow, UK  
E. [emma.danton-rees@succinctcomms.com](mailto:emma.danton-rees@succinctcomms.com)

**ABN Novartis Breakfast Symposium and Debates: Brain Atrophy in MS – A marker in clinical practice?**  
22 May, 2013; Glasgow, UK

**ABN Teva Debate: 'Does progressive disease start on day 1?'**  
24 May, 2013; Glasgow, UK  
E. [emily@bamboo-medical.com](mailto:emily@bamboo-medical.com)

## June

**ENS 2013**  
8-11 June, 2013; Barcelona, Spain  
E. [info@ensinfo.org](mailto:info@ensinfo.org)

**Brain Injury: Common, Disabling and Overlooked Problems. An Interactive Workshop and Discussion with the Experts**  
Tuesday 25th June 2013; London, UK  
Chloe Hayward, E. [info@ukabif.org.uk](mailto:info@ukabif.org.uk)  
T. 0845 608 0788, [www.ukabif.org.uk](http://www.ukabif.org.uk)

**4th Oxford Neurology Course**  
26-28 June, 2013; Oxford, UK  
E. [events@ndcn.ox.ac.uk](mailto:events@ndcn.ox.ac.uk)

**TNA UK Patient & Professionals Conference**  
Saturday 29th June, 2013; London, UK  
[www.tna.org.uk](http://www.tna.org.uk), E. [Naomi.gilbert@tna.org.uk](mailto:Naomi.gilbert@tna.org.uk)

## July

**Human Brain Anatomy**  
15-17 July, 2013; London, UK  
Book online at [www.neurocourses.com](http://www.neurocourses.com)

## August

**EPFL SV- Life Science Symposium: Motor control – from neural circuits and diseases to neuroprosthetics**  
28-30, August 2013; Lausanne, Switzerland  
E. [egizia.carbone@epfl.ch](mailto:egizia.carbone@epfl.ch), T. +41 21 693 96 95,  
<http://lss2013.epfl.ch/index.php>

## September

**NSpine 2013: The UK's Most Comprehensive Spine Course**  
5-7 September 2013; Nottingham, UK  
T. 0800 0 43 20 60, E. [info@nspine.co.uk](mailto:info@nspine.co.uk), [www.nspine.co.uk](http://www.nspine.co.uk)

**BioDynamics 2013**  
– Where Biology, Medicine and Mathematics meet  
11-13 September, 2013; Bristol, UK  
T. +44 (0) 20 8977 7997, E. [biodynamics@conferencecollective.co.uk](mailto:biodynamics@conferencecollective.co.uk)

**Ion Channels in Health and Disease:**  
To celebrate the 50th anniversary of the award of the Nobel Prize to Alan Hodgkin and Andrew Huxley  
16-17 September, 2013; Cambridge, UK  
E. [dg248@cam.ac.uk](mailto:dg248@cam.ac.uk) [www.neuroscience.cam.ac.uk](http://www.neuroscience.cam.ac.uk)

**XXI World Congress of Neurology**  
21-26 September, 2012; Vienna, Austria  
T. +41 22 9080488, E. [Dnuriel@kenes.com](mailto:Dnuriel@kenes.com) [www2.kenes.com/wcn](http://www2.kenes.com/wcn)

## October

**3rd World Parkinson Congress**  
1-4 October, 2013; Montreal, Canada  
T. (+001) 800.457.6676, E. [info@worldpdcongress.org](mailto:info@worldpdcongress.org)  
[www.worldpdcongress.org](http://www.worldpdcongress.org)

## November

**The United Kingdom Acquired Brain Injury Forum 5th Annual Conference**  
21 November, 2013; London, UK  
T. 0845 6080788, E. [info@ukabif.org.uk](mailto:info@ukabif.org.uk) [www.ukabif.org.uk](http://www.ukabif.org.uk)  
**RAatE 2013**  
25 November, 2013; Coventry, UK  
[www.raate.org.uk](http://www.raate.org.uk)

## December

**24th International Symposium on ALS/MND**  
6-8 December, Atahotel Quark Milan, Italy  
E. [symposium@mndassociation.org](mailto:symposium@mndassociation.org), T. 01604 250505

**BNPA December Teaching weekend**  
13-15 December, 2013; Oxford, UK  
T. 020 8878 0573, E. [admin@bnpa.org.uk](mailto:admin@bnpa.org.uk) [orjashmenall@yahoo.com](mailto:orjashmenall@yahoo.com)

## Trigeminal Neuralgia Study Day

SATURDAY 29 JUNE 2013

Grand Connaught Rooms

61-65 Great Queen Street, London WC2B 5DA

*What a difference a vein makes - my TN journey*

Ms Laura Witheridge

*Trigeminal neuralgia differential diagnosis*

Prof. Joanna Zakrzewska, Consultant/Hon Professor Facial Pain Lead, Eastman Dental Hospital

*The McGill Pain Questionnaire - the linguist's view*

Professor Elena Semino, Lancaster University

*Role of cognitive behavioural principles in pain management - application to TN*

Dr Jenna Love, Clinical Psychologist, Eastman Dental Hospital

*Percutaneous interventions and management of recurrences*

Mr Owen Sparrow, Consultant Neurosurgeon, Southampton NHS Trust

*A blood vessel - surely it is more complicated than that?!*

Dr Ken Casey, Neurosurgeon, Detroit, MI, USA

*Medical management of TN and related conditions*

Dr Sam Chong, Consultant Neurologist

*Joint sessions with patients & carers*

*Panel discussion*

*Language and Art of TN*

CPD accreditation applied for

T: 01883 370214, [www.tna.org.uk](http://www.tna.org.uk)

E. [tna@ntlbusiness.com](mailto:tna@ntlbusiness.com)



# RAatE 25 November 2013

Recent Advances in Assistive Technology & Engineering

Conference and Exhibition

University of Warwick Conference Centre, Coventry

## CALL FOR PARTICIPATION

RAatE is the only UK conference focused on the latest innovations in Assistive Technology (AT).

Run in conjunction with Coventry University's Health, Design & Technology Institute (HDTI), RAatE looks to provide news and updates on new technological developments, service innovations, results of formal research projects, service based research and development and a wide range of other stimulating topics

RAatE welcomes papers, posters, case studies and workshops on subjects relating to advances in AT and engineering and this year would particularly welcome those that cover the following topics:

Recreation, use of mainstream technology, factors impacting on AT control and use, how to incorporate evidence based practice

Contributions are welcome from those working in the field of AT or AT users across the full range of products and services designed to enable independence for disabled and older people. If you have a paper or poster that you would like to present that does not fall in to any of the above topics, we would still like to hear from you.

To submit your paper, please visit [www.raate.org.uk/content/submit-a-paper/](http://www.raate.org.uk/content/submit-a-paper/)

Closing date for submissions is **5pm Monday 15th July**

Bath Institute of Medical Engineering



The United Kingdom Acquired Brain Injury Forum

## SPEAKERS AND TOPICS INCLUDE:

Dr David Paynton, National Clinical Lead, RCGP, Centre for Commissioning

How can we improve information and support for GPs to help people with ABI? – A Panel Discussion

Counting the cost of the rehabilitation postcode lottery for road crash victims – Alison Eddy

Sports Related Acquired Brain Injury – Dr Richard Hardie

Mood and Emotional Adjustment after ABI – Dr David Quinn

## The United Kingdom Acquired Brain Injury Forum 5th Annual Conference

Thursday 21st November 2013

The Royal College of General Practitioners, 30 Euston Square, London, NW1 2HD

The United Kingdom Acquired Brain Injury Forum | PO Box 159 | Launceston | PL15 0AW

T.0845 6080788 E.[info@ukabif.org.uk](mailto:info@ukabif.org.uk) [www.ukabif.org.uk](http://www.ukabif.org.uk)

To see the full programme or to make a booking please visit our website or email Chloë Hayward at [info@ukabif.org.uk](mailto:info@ukabif.org.uk)

## 2012 ACRM Annual Conference

## Progress in Rehabilitation Research

*Conference details:* 9-13 October, 2012, Vancouver, Canada. *Report by:* Sakel Mohammed, East Kent Hospitals University NHS Foundation Trust.

The 2012 American Congress of Rehabilitation Medicine (ACRM) annual congress "Progress in Rehabilitation Research" was held in the tranquil city of Vancouver. It was considered the most successful event in ACRM's 89 year history. There were about 700 attendees from more than 27 countries.

The programme was packed with diverse topics catering for most senior staff to trainees and academicians to clinicians. The global leaders in their field presented their results from cutting edge research programmes in; brain injury, spinal cord injuries, neuromodulation, disorders of consciousness, outcome measures, pain management, spasticity management and socio-political aspects of rehabilitation programmes in the changing landscape of health care policies in the world. There were pre-conference courses for in-depth teaching on "Evidence, Theory and Experience: implementing Evidence into Rehabilitation Practice".

Dr G R Ulicny moderated a session where it was debated how long the rehabilitation programme should be. Should it be limited to 2 years? The initial short perspectives were presented by stakeholders including patient associations, insurance agencies, federal

government, a medical director and a Canadian researcher representing the Canadian Institute of Health Research (CIHR).

The main theme seemed to be the strategic decision of ACRM to have an outward looking approach. There was a discount for international attendees which may account for 260 delegates from outside the USA. Various networking groups were formed, for example the "Outcome Measurement Networking Group", which invited participants to propose a topic for the next conference.

Perhaps the most significant development was the formation of the "International Networking Group" (ING) which was attended by the most senior ACRM Committee members.

ACRM pledged their interest in promoting cross-border collaboration in rehabilitation research, developing shared ideals and



promoting other international rehabilitation conferences on their website. The latter was approved during the meeting and a little known event organised by International Rehabilitation Forum (IRF) was on the ACRM website within days! That IRF programme was at Dhaka in December 2012 on the theme of "developing Rehab services in low resource countries". The ACRM has now pledged to dedicate 1 symposium to the International Networking Group in the 2013 Conference. This will explore how cross border collaborative research could be facilitated and how best to tap into the EU research fund which is under spent and insists upon multinational diverse partnership.

The conference had excellent feedback. 92% of attendees said that they were satisfied or more than satisfied with the knowledge and expertise of the faculty. 87% said the overall quality of education was good to excellent.

ACRM encourages membership. Membership benefits include free hard copies of the Journal "Archives of PMR" and a reduced rate for conference registration fees and often free registration at the mid-year conference. For more details see <http://www.acrm.org/>. The 2013 conference will be on 12-16th November at Orlando, Florida near Disneyworld. ♦

## PREVIEW 5th Annual UKABIF Conference

*Conference details:* 21st November 2013, London, UK.

London's new headquarters for the Royal College of General Practitioners (RCGP) at 30 Euston Square will be the venue for the 5th Annual United Kingdom Acquired Brain Injury Forum (UKABIF) Conference on the 21st November 2013. The state-of-the-art conference facility, adjacent to Euston Station, will host speakers from the medical and legal world presenting on topics such as the impact of commissioning, the rehabilitation service postcode lottery, sports-related acquired brain injury and post-injury adjustment of mood and emotion.

The meeting will be of interest to a diverse target audience from doctors in primary and secondary care, all members of the rehabilitation multidisciplinary team, case managers, personal injury lawyers, social care workers, voluntary organisations and care providers.

Dr David Paynton, National Clinical Lead at the RCGP Centre for Commissioning will discuss the implications of commissioning neurorehabilitation services eight months into the financial year. He will be reviewing the risks

and opportunities for primary care, the demographic pressures and how the community teams are integrated. Alison Eddy, Partner at Irwin Mitchell, the personal injury law and rehabilitation specialists, will present the company's recently published research highlighting the fact that annually more than 13,000 of the most seriously injured road collision victims face a rehabilitation postcode lottery (see feature on page 29 of this issue of ACNR).

A section of the award winning documentary film 'Head Games' will be screened and Dr Richard Hardie, a Consultant Neurologist at North Bristol NHS Trust with a special interest in sport concussion will look at the issues surrounding sports-related acquired brain injury. Following a presentation from an individual with an acquired brain injury and his wife, Dr David Quinn will discuss the assessment and management of the mood and emotional changes following acquired brain injury.

There will also be an interactive panel and audience discussion to look at ways of improving the information and support tools

required by GPs for managing their patients with acquired brain injury. Perhaps the much needed follow-up of these patients could originate in primary care if the medical teams had the necessary training, monitoring and follow-up guidance?

Attendees will also hear more about UKABIF's Campaign 'Life after Brain Injury? Improve Services Now' launched last year to highlight the need for improvements in the provision of services for people with acquired brain injury.

The two prestigious UKABIF Awards – UKABIF Award for Innovation and the UKABIF Award for Inspiration will also be presented at the Conference and both are now open for nominations with a deadline for entries of the 18 October 2013. ♦

More details about the programme and how to register for the conference can be found on the UKABIF website:  
[www.ukabif.org.uk](http://www.ukabif.org.uk).

# NeuroPACES, The Walton Centre MRCP PACES Neurology Course

**Conference details:** 9-13 October, 2012, Vancouver, Canada. **Report by:** VLM Yip, MRC Clinical Fellow in Clinical Pharmacology and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, The Wolfson Centre for Personalised Medicine, University of Liverpool.

NeuroPACES is an intensive one day clinical teaching course organised by the Walton Centre for Neurology and Neurosurgery in Liverpool which focuses on the neurological station of the MRCP Part 2 Clinical Examination (more commonly known as PACES - Practical Assessment of Clinical Examination Skills). PACES is an essential qualification for all physicians and a pre-requisite for completion of core medical training (CMT). As a junior doctor I felt that the neurology station was the most difficult to prepare for. This was through a combination of limited experience, as many neurological cases encountered in PACES tend to be managed in specialist neurologist centres that junior doctors have limited access to, and eliciting and interpreting neurological signs can be difficult without having experienced these cases in real life.

Several PACES teaching courses exist, organised by both hospital trusts and commercial companies, designed to prepare candidates for all aspects of the examination. I had attended one of these courses in London but felt that the course did not provide adequate breadth of neurological presentations encountered in the examination or dedicate enough time and supervision for me to feel confident at neurological examination, presentations and diseases. This was my motivation to attend NeuroPACES.

There were approximately 30 delegates who attended the NeuroPACES course. Most were UK based junior medical trainees preparing for the

PACES examination although a few delegates had travelled from abroad especially to attend the course. Some of the delegates had failed the exam previously whilst others were preparing for their first attempt at the PACES examination.

The morning began with a lecture by a professor in neurology and neurology registrar explaining how to approach the neurology station in PACES and demonstration of the neurological examination. This ensured that every candidate can perform a neurological examination as expected by the neurologist. All participants were also provided with a booklet reviewing the examination and neurology cases with tips for the real exam and areas to make notes from the course.

Candidates were then divided into groups of 4-6 and rotated through 24 neurological cases with time for examination, presentation, teaching and feedback. The whole day was undertaken in a mock exam format, just like the MRCP PACES stations, with 6 minutes to examine and 4 minutes for questions; but this is then followed by 5 minutes per case for the training neurologist to demonstrate missed signs, provide feedback and explain how to improve. Each participant got to practice every examination, elicit important clinical signs and present their findings as well as have their questions addressed. Neurological presentations included multiple sclerosis and fascioscapulo-humeral dystrophy in the limb examination, myotonic dystrophy and retinitis pigmentosa in cranial nerve examination and parkinson's plus

syndromes and choreoathetosis in the movement disorder section.

As a 1st year CMT trainee preparing for the PACES examination for the first time the NeuroPACES course was definitely worth attending. The variety of the cases was exceptional as some cases, such as progressive external ophthalmoplegia and Brown-Sequard syndrome, I had only read about in text books and never encountered in clinical practice. All of the faculty members were knowledgeable, friendly and experienced in the PACES examination. I practiced all of the examinations, elicited all of the signs and presented my findings as in the real examination.

I passed my PACES examination first time and achieved full marks in the neurology station, which was a complex cranial nerves examination, thanks to this course. I would recommend NeuroPACES to all medical trainees preparing for their PACES examination. Prospective candidates should book the course and study leave early and review the neurology cases from a PACES textbook prior to attending to ensure that they get maximum benefit from the course. ♦

Further information  
More information about the course is at  
<http://www.liv.ac.uk/neurosciences-research-unit/neuropaces/>  
Competing interests: None declared.

## Britannia launches innovative and interactive resource for PD patients and carers

World Parkinson's Day 2013 saw the official launch of *theparkinsonhub* ([www.theparkinsonhub.com](http://www.theparkinsonhub.com)), an online community based on sharing the latest news and best practice about Parkinson's disease (PD), with an emphasis on and around mid to late stage PD.

Developed by Britannia Pharmaceuticals, *theparkinsonhub* is a dynamic, evolving resource committed to providing practical help and advice to maximise patient well-being. It is regularly updated on a range of key areas of life that cover both motor and non-motor symptoms of PD.

This is accompanied by the launch of a complementary PD Quality of Life interactive resource ([www.pdqualityoflife.com](http://www.pdqualityoflife.com)) which enables people with PD to identify and understand those areas in their life most impacted by their condition. They are then empowered to have a more informed discussion about their well-being and unique needs with their healthcare professionals (HCPs) and care teams.

At the heart of theparkinsonhub and the PD Quality of Life

resource is the recognition that no two people's experience of PD is the same. However, with the right support and information it is possible for those with PD to live with confidence and control. Both have been designed in conjunction with HCPs to help provide this information and to be an external resource that HCPs can confidently direct their patients towards.

"Where theparkinsonhub excels is in consistently focusing on the person first and their PD second. By addressing the impact on a person's well-being in terms of non-motor as well as motor symptoms, it has a much more holistic approach to meeting people's needs with regards to their quality of life. From an HCP perspective, the more someone understands their unique PD journey, the easier it is to have an informed discussion about how best to address their unique quality of life challenges and to help them live in confidence and control," says Anne Martin, a Parkinson's nurse.

*Anne Martin has been a Parkinson's nurse for 11 years with 20 years' wider experience working in neurology, including PD.*



**Colin Ettinger,**

*LLB (Hons)* is a rehabilitation and serious injury law partner with Irwin Mitchell. He has over 30 years' experience representing serious injury victims and is a vice-president of the College of Occupational Therapists. He is also an honorary research fellow at the School of Law at Lancaster University.



**Emma Hawe,**

*MSc Applied Statistics* is Head of Statistics at OHE Consulting. She has published in excess of fifty peer reviewed publications. Emma has advised various organisations, including the Department of Health on her research interests, which include statistical methods for the assimilation and analysis of health related data.



**Sarah Karlsberg Schaffer,**

*MSc Economic Policy* is an economist at OHE Consulting. Her research interests include the relationship between formal and informal care and the economic effects of the ageing population. She is also interested in investment decisions in the NHS, applied industrial organisation and labour economics.



**Lesley Baillie,**

*BA (Hons) Public Administration* has been involved in the collation of health statistics for over 20 years and has considerable experience in the availability of sources of health and healthcare information in all countries of the UK and in conducting systematic literature reviews.

# Is There a Rehabilitation Postcode Lottery?

In 2011, over 13 thousand people suffered a serious injury as a result of a road traffic collision (RTC) and required three or more days' stay in hospital (likely requiring rehabilitation). There are an estimated 1 million people living with the consequences of brain injury in the UK,<sup>2</sup> which is reported to be associated with increased vulnerability to death for at least 13 years post-injury.<sup>3</sup> But research carried out by OHE Consulting, on behalf of serious injury and rehabilitation specialist law firm, Irwin Mitchell, reveals that current rehabilitation provision can be a postcode lottery.

While there are programmes underway that are helping to improve access to specialist rehabilitation services, such as UK Rehabilitation Outcomes Collaborative (UKROC) and TARN databases, patients in some areas can't access the right rehabilitation services, with a four-fold difference in the interquartile range between reported rate of specialist inpatient rehabilitation services for head injuries at the Primary Care Trust (PCT) level,<sup>4</sup> amongst those that record rehabilitation episodes, (Interquartile range 1.4,6.8 per 100,000 population).

Our research, *Counting the cost of the rehabilitation postcode lottery for road crash victims*,<sup>5</sup> draws together information from a range of sources, including the latest available Hospital Episodes Statistics (including PCT level data from 2010/2011 and 2011/2012), rehabilitation studies from different countries and the experiences and recommendations of rehabilitation healthcare professionals. It builds a national picture of use and demand for rehabilitation services across England. This review focuses on brain injuries, and those injuries sustained in RTCs.

A key finding from our research was the discrepancies and inconsistencies in the way that information about rehabilitation services is recorded, necessitating the consultation of multiple data sources.

Our research included a series of recommendations, outlined at the end of this review, and suggests that co-ordinated and intensive rehabilitation could save the NHS money; improve patients' recovery prospects and the emotional well-being of their carers; and help patients to play a more active role in society.

**Demand for rehabilitation services**

In 2011/12 there were 151,678 patients admitted to hospital in England following a head injury, equivalent to 285.5 per 100,000 population.

Table 1 shows that 16,551 of these individuals were admitted to a hospital in England for three or more days and may be considered likely to require rehabilitation in 2011/12. Estimates in the literature relating to the proportion of head injuries which result from RTCs is variable. Wade *et al*<sup>6</sup> reported that over two-in-five admissions for head injuries were as the result of an RTC. In contrast a study by Thornhill<sup>7</sup> noted that just 11% were injured due to an RTC. Pulling together available information relating to underlying external cause coded for head injury admissions to hospital in England in 2011/12, around 1 in 13 were recorded as being as the result of a RTC.

**Variation in brain injury admissions at regional level**

Tennant<sup>8</sup> has explored variation in inpatient admissions for brain injuries for all causes at PCT level and considered underlying factors which may influence admissions rates. It noted that regional differences may result from underlying factors such as rural and urban locations and the level of deprivation.

Variability is observed in the per-population rate of patients admitted as an emergency in England in 2011/12 at PCT level (Interquartile range 178, 515).<sup>10</sup> A correlation between the per-population rates of emergency admissions for head injuries for 2010/11 and 2011/12 is observed at a PCT level, indicating underlying factors other than the population size affect the number of admissions. Figure 1 demonstrates the high level of variability, and also indicates that underlying factors may not be adequately accounted for through the calculation of expected rates, using only the population size of the PCT. This casts doubts on the appropriateness of the confidence limits.<sup>11</sup> Variation was also seen when considering only those admissions resulting from RTCs, with an interquartile range from 12 to 38. This indicates the variability in admissions for head injuries at PCT level resulting from an RTC, which is not explained by differences in the underlying population size.

**Rehabilitation access**

There is limited evidence on access to rehabilitation services in England. Information tends to be based on small studies of patient subsets. However, rehabilitation specialists have highlighted a perceived lack of rehabilitation capacity, and a number of sources

	2010/11	2011/12
Number of admissions	161,469	161,909
Number of patients	151,261	151,678
Rate of patients admitted per 100,000 population	287.1	285.5
Number of patients admitted with 3 or more days stay in hospital	15,955	16,551
Rate of patients admitted with a stay of 3 or more days per 100,000 population	30.0	31.2

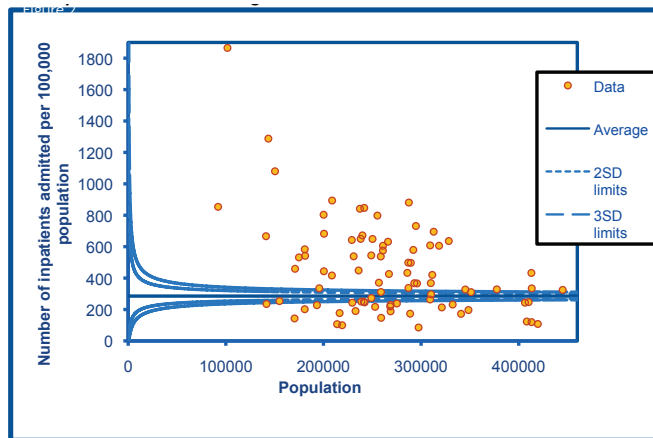


Figure 1: Funnel plot of rate of patients admitted per 100,000 population for head injuries at PCT level, by PCT of treatment in England, 2011/12.

Notes: expected activity is based on population sizes and the national rate of rehabilitation episodes. The level of dispersion suggests that there are some underlying factors which are not properly accounted for.

(a survey of PCTs and initial findings from a trial of rehabilitation services following intensive care) indicated fragmentation and lack of access to specialist services for those with long-term neurological conditions.<sup>13</sup>

There was a weak relationship between patient admissions for head injuries with a 3+ days' stay and the number of patients receiving rehabilitation treatment under a rehabilitation consultant for head injuries in England in 2011/12. Inpatient admissions for rehabilitation for head injuries were found to be variable at PCT and SHA level. Rates of head injury rehabilitation admissions per population and per emergency admissions were also found to vary at PCT level.

Roundtable discussions with rehabilitation specialists suggested that access to vocational rehabilitation varies across England for those suffering an acquired brain injury, with clusters in London, the Midlands, the North of England and Scotland, but a lack of facilities in the South West of England.

### Challenges facing delivery of rehabilitation services

Discrepancies and inconsistencies in the recording of information are compounded by a lack of resources, co-ordination of care pathways and disjointed funding, exacerbating access issues.

#### 1. Resources

Rehabilitation healthcare professionals indicated that resource challenges meant that rehabilitation is often not sustained for long enough to allow a patient to continuously improve. In some cases, for example for neuropsychiatric rehabilitation, there are simply not enough services available.

One of the most common concerns was that community care is insufficient, or short-lived, with some specialists reporting that community care for a serious injury patient seemed to drop off after the first six months. One contributing factor that was suggested was a high turnover of community care staff.

#### 2. Continuity and coordination of care pathways

A lack of continuity and coordination of care as patients are transferred from one service to another was highlighted as a key barrier to effective rehabilitation.

In the first phase of treatment, the healthcare team who treat a patient may not have the expertise to assess the long term impact of a patient's injuries and their continuing care needs. This increases the risk of delay in getting the care pathway and specific rehabilitation requirements right. Beyond this, many attendees recounted experiences of a delay in transferring patients from an acute hospital setting to a specialist rehabilitation unit.

### 3. Disjointed funding

Historically, effective access to rehabilitation has also been hampered by disjointed and conflicted funding bodies, eg PCTs and social services, which mean that the financial support offered to some patients can be too little, too late. It will be interesting to see how this is addressed under Clinical Commissioning Groups.

Rules concerning when funding can be released, on the basis of a patient having met particular goals set for them, can also slow and stem the provision of adequate financial support.

### Recommendations

Based on our full analysis, we can surmise that serious injury patients need more coordinated and sustained care. By getting patients into rehabilitation more quickly, and taking a more holistic view of his/her needs – from rehabilitation (whether on the NHS or through private companies and funded by compensation from litigated cases) through to in-home care and support in accessing Local Authority and charity services – we can improve functional recovery prospects.

We have drawn a number of recommendations to help improve access to specialist rehabilitation services and care:

1. Record rehabilitation data in a consistent way across all English Clinical Commissioning Groups to allow for easy comparison, eg by expanding the UKROC database to include community level data
2. Identify best practice and demonstrate the financial benefits to secure further funding
3. Calculate the life-long rehabilitation needs of patients, and pool funding to deliver it through a single body
4. Improve care for people once they are back at home through more specialist community rehabilitation services

While some initiatives have been put in place which are beginning to better integrate services more effectively, and improve quality of care, our research suggested that much more needs to be done.

To receive the full report *Counting the cost of the rehabilitation post-code lottery for road crash victims*, please email: lynne.carrick-leary@irwinmitchell.com

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## AM IMPAKT – New clinical trial investigates apomorphine injection for resolving morning akinesia in Parkinson's disease patients

AM IMPAKT, (Apokyn for Motor IMProvement of Morning AKinesia Trial), is a Phase IV, multi-center, open-label study investigating treatment with APOKYN (APO-go/Apomine) injection to achieve rapid and reliable improvement of motor symptoms in Parkinson's disease (PD) patients who experience delayed onset of their oral levodopa medication taken upon awakening. A sub-study will also investigate how gastrointestinal (GI) symptoms, commonly experienced by PD patients, may contribute to this delayed onset of effect.

PD patients experience motor fluctuations resulting from the brain's decreasing ability to maintain a consistent level of dopamine. The states of motor function in PD patients are referred to as 'ON' and 'OFF', and most patients are on a treatment regimen designed to limit the amount of 'OFF' time they experience with medicines such as levodopa that impact dopamine production. Up to half of all patients receiving levodopa can develop symptoms of 'wearing off' within two years of starting levodopa therapy.<sup>3</sup> Also, impaired motor function can often occur in PD patients as a result of unreliable onset of therapeutic effect after taking a dose of oral medication; this is referred to as 'delayed ON' and when it occurs upon awakening is referred to as 'morning akinesia'. Symptoms of morning akinesia include slowness, stiffness, freezing and falls, and can have a significant impact on the subject's ability to carry out their normal daily morning activities.

Some degree of GI dysfunction is common in PD patients as part of the disease process, including gastroparesis, where the stomach takes longer than normal to empty. Gastroparesis is common in both early and advanced PD; in fact it has been suggested that delayed gastric emptying may be a marker of preclinical PD. A survey of PD patients found that 24% reported nausea and 45% reported bloating, both symptoms of gastroparesis.<sup>1</sup> Despite its frequency, gastroparesis often goes unrecognised in PD.

As a potent dopaminergic agonist which is administered subcutaneously and therefore bypasses the GI tract, APOKYN (APO-go) is expected to have the ability to raise dopamine levels even if gastric emptying is slowed as a result of PD. The hypothesis that delayed-ON episodes with oral PD medication may be due to either gastroparesis or to impaired intestinal absorption will be explored as part of the AM IMPAKT study.

Stuart H Isaacson, MD (Associate Professor, Florida International University Herbert Wertheim College of Medicine, Miami FL; Director, PD and Movement Disorders Center of Boca Raton; Research Director, Marcus Neuroscience Institute, Boca Raton Regional Hospital), the lead investigator on AM IMPAKT, commented:

"We are very excited to have commenced this important study. Our first patient was recruited in December and we plan to have initial results available in August. We hope to show that APOKYN (APO-go) will provide a valuable treatment option for PD patients with morning akinesia due to delayed onset of levodopa by rapidly and reliably restoring their motor function and enabling them to get on with their day."

APOKYN (APO-go) injection has been shown in previous clinical studies to provide rapid and reliable improvement in motor symptoms of PD;<sup>2</sup> Mean changes from baseline were seen at 20 minutes with some changes being seen as early as 10 minutes following injection.

For more information see [www.britannia-pharm.com](http://www.britannia-pharm.com)

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## Stannah and Horizon MDs Join New Expert Panel



Jason Tate, Director  
– Help My Mobility

Patrick Stannah, Joint MD  
– Stannah Stairlifts

Graham Billcliffe, Director  
– Horizon Mobility & Mobility Hire

The MDs of two of the UK's leading mobility equipment providers have joined a new expert panel, aiming to offer advice and support to individuals with mobility equipment quandaries.

Patrick Stannah, the MD of the family owned Stannah Stairlift firm, has years of experience, and could not be in a better position to offer advice. He is joined by Graham Billcliffe, MD of Cheltenham based Horizon Mobility. Graham is an expert in a wide range of mobility equipment, and well versed in the mobility aid hiring process.

The panel is completed by Jason Tate, Director of Help My Mobility, the online mobility equipment resource which will host the expert panel. Mr Tate was keen to assemble the expert team as a way to

improve the usefulness of Help My Mobility's service to its visitors.

"We're constantly looking for ways to further develop our service in order to make it as effective as possible for our users," he said.

"One of the key tenets of our site is its transparency, and easy manner in which its information can be accessed. By creating an Ask The Expert panel, we are able to streamline our user experience even further, giving them direct access to some of the most knowledgeable figures in the industry."

A link to the Ask An Expert page can be found on Help My Mobility's home page at [www.help-my-mobility.org](http://www.help-my-mobility.org)

# An element of change

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1. Gunthorpe M et al. *Epilepsia* 2012; 53: 412-424.

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retigabine tablets

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Friday 7<sup>th</sup> June 2013 – Queen Square, London  
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### Trobalt<sup>®</sup> (Retigabine) Prescribing Information

(Please refer to the full Summary of Product Characteristics before prescribing).

**Presentation** Trobalt tablets<sup>®</sup> each containing retigabine equivalent to either: purple film coated round tablets containing 50 mg retigabine; green film coated round tablets containing 100 mg retigabine; yellow film coated oblong tablets containing 200 mg retigabine; green film coated oblong tablets containing 300 mg retigabine; purple film coated oblong tablets containing 400 mg retigabine. **Indications** Adjunctive treatment for partial onset seizures with or without secondary generalisation in adults aged 18 years and above. **Dosage and Administration** Trobalt must be taken orally in three divided doses each day. The maximum total daily starting dose is 300 mg (100 mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week according to individual patient response and tolerability. An effective maintenance dose is expected between 600 mg/day and 1,200 mg/day. **Renal impairment:** No dose adjustment is required in patients with mild renal impairment. A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min). The total daily starting dose is 150 mg, and it is recommended that during the titration period the total daily dose is increased by 50 mg every week to a maximum total dose of 600 mg/day. **Hepatic impairment:** No dose adjustment is required in patients with mild hepatic impairment. A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe hepatic impairment (Child-Pugh score ≥7). The total daily starting dose is 150 mg and it is recommended that during the titration period the total daily dose is increased by 50 mg every week to a maximum total dose of 600 mg/day. **Elderly** (65 years of age and above): A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients. The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended. **Contra-indications** Hypersensitivity to retigabine or any of its excipients. **Special warnings and precautions** Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine generally within the first 8 weeks of treatment. Trobalt must be used with caution in patients at risk of urinary retention and it is recommended that patients are advised about the risk of these possible effects. Caution should be taken when Trobalt is prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients it is recommended that an electrocardiogram (ECG) is recorded before initiation of treatment with Trobalt and in those with a corrected QT interval > 440 ms at baseline, an ECG should be recorded on reaching the maintenance dose. Psychiatric disorders: Confusional state, psychotic disorders and hallucinations were reported in controlled clinical studies. It is recommended that patients are advised about the risk of these possible effects. **Suicide risk:** Suicidal ideation and behaviour have been reported in patients treated with anti epileptic agents in several indications. Patients (and caregivers of patients) should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge. **Elderly** (65 years of age and above): Elderly patients may be at increased risk of central nervous system events, urinary retention and atrial fibrillation. Retigabine must be used with caution in this population with a reduced initial and maintenance dose recommended. As there is individual variation in response to all antiepileptic drug therapy, it is recommended that prescribers discuss with patients the specific issues of epilepsy and driving. **Overdose** In the event of overdose it is recommended that the patient is given appropriate supportive

therapy as clinically indicated, including ECG monitoring. Further management should be as recommended by the national poisons centre, where available. **Fertility, pregnancy and lactation** Trobalt is not recommended during pregnancy and in women of childbearing age not using contraception. It is unknown whether retigabine is excreted in human breast milk. The effect of retigabine on human fertility has not been established. **Drug interactions** *In vitro* data indicated a low potential for interaction with other antiepileptic drugs. Pooled analysis from clinical studies showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance. Steady-state data from a limited number of patients in smaller studies indicate that phenytoin and carbamazepine could reduce retigabine systemic exposure by 35% and 33% respectively. Trobalt interaction with digoxin of therapeutic doses may increase digoxin serum concentrations. Retigabine may increase the duration of some anaesthetics. Up to 750 mg/day, no clinically significant effect on pharmacokinetics (PK) of combined oral contraceptive pill (COC). Low dose COC did not significantly affect PK of retigabine. Advise patients that alcohol may lead to blurred vision. **Adverse reactions** A dose relationship seems to exist between dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation. **Metabolism and nutrition disorders:** common: weight increase, increased appetite. **Psychiatric disorders:** common: confusional state, psychotic disorders, hallucinations, disorientation, anxiety. **Nervous system disorders:** very common: dizziness, somnolence, common: amnesia, aphasia, coordination abnormal, vertigo, paraesthesia, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation. **General disorders and administration site conditions:** very common: fatigue, common: asthenia, malaise, peripheral oedema. **Basic NHS costs** Initiation packs of 21 x 50 mg tablets and 42 x 100 mg tablets (EU/1/11/681/013) is £24.33. Maintenance packs of 21 and 84 x 50 mg tablets are (EU/1/11/681/001) \$4.87 and (EU/1/11/681/002) \$19.46 respectively. Maintenance packs of 21 and 84 x 100 mg tablets are (EU/1/11/681/004) \$9.73 and (EU/1/11/681/005) \$38.93 respectively. Maintenance packs of 84 x 200 mg tablets are (EU/1/11/681/007) \$77.86. Maintenance packs of 84 x 300 mg tablets are (EU/1/11/681/009) \$116.78. Maintenance packs of 84 x 400 mg tablets are (EU/1/11/681/0011) \$127.68. **Legal category:** POM **Marketing authorisation holder** Glaxo Group Limited, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, United Kingdom. **Further information is available from:** Customer contact centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. Email: [customercontactuk@gsk.com](mailto:customercontactuk@gsk.com) Customer Services Freephone 0800 221441. **Trobalt**<sup>®</sup> is a registered trademark of the GlaxoSmithKline group of companies. All rights reserved. **Prescribing information last revised** November 2012  
UK/RTG/0107/12

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to GlaxoSmithKline on 0800 221 441

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