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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

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RAPID RELIABLE 'ON' FOR PARKINSON'S DISEASE

APO-go® Apomorphine hydrochloride
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 (4-12 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals, as with levodopa, when given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders, including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating, can occur in patients treated with dopamine agonists, including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and broncospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection, leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely, injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually transient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests, haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine. 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, compulsive spending or buying, binge eating or compulsive eating, (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported, as has peripheral oedema. Apomorphine has been associated with sudden sleep onset episodes. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 04483/0072 APO-go Pens: PL 04483/0073 APO-go Pre filled syringes: PL 04483/0074 **Legal Category** POM **Date of last revision:** April 2015 For further information please contact: Britannia Pharmaceuticals, 200 Longwater Avenue, Green Park, READING, Berkshire, RG2 6GP

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information on 0870 851 0207 or dso@britannia-pharm.com

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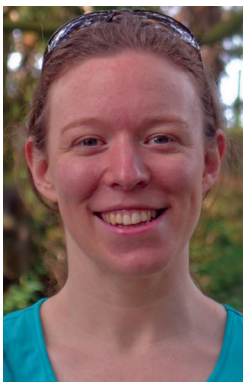
Alzheimer's Society Chief Executive presented with CBE for services to older people

Jeremy Hughes, Chief Executive of Alzheimer's Society, has been presented with a CBE for services to older people by Her Majesty the Queen. Jeremy has been Chief Executive of Alzheimer's Society since 2010. During Jeremy's time at Alzheimer's Society, he has succeeded in significantly raising the profile of dementia among the general public and to political leaders on the world stage. Alzheimer's Society worked hard to shape the agenda for the 2013 G8 summit, which was dedicated to tackling dementia. Jeremy has also steered a major shift in society's attitudes towards people with dementia. He co-chairs the Dementia Friendly Communities Champion Group which works to develop dementia friendly communities. Jeremy has also overseen the creation of Alzheimer's Society's Dementia Friends initiative, the biggest ever social action movement to change perceptions of dementia, which was one of the many reasons for the Society's recent achievement of being named 'Britain's Most Admired Charity' at this year's Third Sector Awards.

Professor Tony Holland awarded a CBE

Professor Tony Holland has been awarded a CBE on the 2015 Queen's Birthday Honours list for services to psychiatry. He is Professor of the Psychiatry of Learning Disabilities and Head of the Cambridge Intellectual and Developmental Disabilities Research Group in the department of Psychiatry. His main areas of research include the relationship between genetic syndromes and associated psychiatric and behavioural disorders, and clinico-legal studies. He is also Chair in Learning Disabilities at the Health Foundation, Fellow and Vice-President of the International Association for the Scientific Study of Intellectual Disability, President of the UK Prader-Willi Association, and President of Cambridge MENCAP.



Sian Alexander, Co-Editor.

This issue of ACNR is focused on the interface between Neurology and Psychiatry. Consisting of often fascinating patients, unresolved aetiologies and intense research, there are frequent areas of overlap between the two specialisms where once there was the mind: brain divide. The e-newsletter for this issue of ACNR is being distributed to about 4000 members of the Faculty of Neuropsychiatry in addition our own 2900 e-readers and we hope you enjoy it.

As evidenced by articles in this issue, psychiatric issues often affect patients seen in neurological practice. Patrick Williams describes the psychological impact of terrible pain in the form of trigeminal neuralgia and the relief achieved from neurosurgery. Marco Mula discusses neuropsychiatric symptoms in epilepsy. Individuals with epilepsy frequently report psychiatric symptoms, particularly mood disturbance, and psychotic symptoms may also be part of the epilepsy syndrome. Regina Katzenschlager provides a highly practical review of apomorphine in Parkinson's disease.

Camilla Nord and Jonathan Roiser review some heartening evidence for transcranial direct current stimulation applied to the dorsolateral prefrontal cortex as a new treatment for depression. If effective, this 'neurally administered' treatment would explicitly bind our understanding of disordered mood to neural function, and potentially enrich our understanding of the biological basis of affective disorders.

David Werring and Steven Greenberg present a thoughtful account of a life well lived: Dr Miller Fisher. I admit to knowing nothing about this impressive neurologist before reading this article beyond the Guillain Barre Syndrome variant that bears his name. I am captivated by the wisdom of Fisher's Rules, his many achievements, and his enthusiasm for practicing clinical neurology even when nearly ninety years old. His advice to 'study the patient seriously' is grounding advice for those of us in clinical training and clinical research alike.

There are two CBE awards to mention from earlier in the year: Jeremy Hughes, Chief Executive of Alzheimer's Society, and Tony Holland, Professor of the Psychiatry of Learning Disabilities, University of Cambridge. Appropriately enough, the work of both individuals is of a neuropsychiatric flavour: congratulations to you both.

And for anyone wondering about the new face at the top of the Introduction: fear not, Mike will return to his usual place in the next issue!

Sian Alexander, Co- Editor
Email. Rachael@acnr.co.uk

1. Fisher CM. *The Origin of Miller Fisher Syndrome*. ACNR 2005;5(5):12. www.acnr.co.uk/pdfs/volume5issue5/v5i5millerfisher.pdf

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CRIT/07/2015/368 Date of preparation: July 2015

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Prescribing Information. Please refer to the Summary of Products Characteristics (SPC) before prescribing. Presentation: An off white viscous suspension with a raspberry odour, containing 5 mg or 10 mg of clobazam per 5 ml of suspension. **Indications:** Clobazam may be used as adjunctive therapy in epilepsy. Clobazam is also indicated in the treatment of anxiety. Please refer to the SPC for further information. **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.* ***Treatment of epilepsy in association with one or more other anticonvulsants:*** In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily. The patient must be re-assessed after 4 weeks and regularly thereafter to evaluate the need for continued treatment. It is recommended to gradually decrease the dosage. *Elderly:* Doses of 10-20 mg daily. Treatment requires low initial doses and gradual dose increments under careful observation. *Children:* Children require low initial doses with gradual dose increments under careful observation. It is recommended that normally treatment should be started at 5mg daily. 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. ***Treatment of anxiety:*** Please refer to the SPC for information on dosage and administration. **Contra-Indications:** Patients with hypersensitivity to benzodiazepines or any of the excipients of clobazam; patients with any history of drug or alcohol dependence, myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic insufficiencies, 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:** Amnesia may occur with benzodiazepines. In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines. Use with extreme caution in patients with personality disorders, myasthenia gravis, spinal or cerebellar ataxia or sleep apnoea; chronic or acute severe respiratory insufficiency; impaired renal or hepatic function; reduce dose if necessary. Use of benzodiazepines may lead to the development of physical and psychological dependence therefore the duration of treatment should be as short as possible. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Consult SPC for further information. **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. 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 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, they may have developed physical dependence and may be at risk for developing postnatal withdrawal symptoms. 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 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 this event, 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 (eg, 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. Consult SPC for further information. **Product Licence Number:** PL 00156/0322 (5 mg/5 ml), PL 00156/0323 (10 mg/5 ml). **Product Licence Holder:** Martindale Pharmaceuticals Ltd T/A Martindale Pharma, Bampton Road, Harold Hill, Essex RM3 8UG. **Basic NHS Price:** £90.00 (5 mg/5 ml); £95.00 (10mg/5ml). **Legal Category:** POM. Further information: Martindale Pharma, Bampton Road, Romford, RM3 8UG. Tel: 01277266600. **Date of Preparation:** July 2015.

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References:
1. Tapclob 5mg/5ml Summary of Product Characteristics and Tapclob 10mg/5ml Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc /
2. MHRA. Antiepileptic drugs: new advice on switching between different manufacturers' products for a particular drug. Letter to healthcare professionals from the Commission on Human Medicines November 2013.

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Neuropsychiatric symptoms in epilepsy: an overview

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Epilepsy is amongst the most common neurological conditions with incidence rates, in developed countries, ranging between 40 and 70/100,000 persons/year and even higher rates in children and elderly people. As captured by the new definition,[1] epilepsy is now recognised as a disorder of the brain characterised not only by recurrent seizures, but also by its neurobiological, cognitive, psychological and social consequences. For a long time the mutual relationships among epilepsy, seizures and behaviour have been matter of debate, fascinating generations of clinicians and neuroscientists. In his famous quotation, Hippocrates reported that "melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy". This early observation has been recently revitalised by modern epidemiological studies pointing out a bidirectional relationship between epilepsy and psychiatric disorders.[2]

In general terms, psychiatric problems show a uniformly increased prevalence in epilepsy as compared to the general population[3] (Table 1). In some cases, this partially reflects the severity of the seizure disorder as prevalence rates are higher in subjects with refractory syndromes as compared to patients with well controlled epilepsies but in other cases the clinical scenario is more complex than that.[4] In fact, for example, a population-based study showed that the rate ratio of suicide in people with epilepsy remains doubled even after excluding patients with psychiatric comorbidities and adjusting for various factors.[5] Data from the SANAD trial showed that newly diagnosed untreated patients with epilepsy are already cognitively compromised before any treatment is started, independently by the underlying cause.[6] It is clearly evident that epilepsy is characterised by a number of clinical manifestations that comprise also cognitive and behavioural symptoms that, in same selected cases, can even precede the onset of seizures themselves.

As any epileptologist is aware of, treatment and prognosis of epilepsy rely on the accurate identification of the specific syndrome defined by a collection of clinical variables (e.g. age of onset, seizure pattern) and laboratory findings (e.g. EEG and MRI). Although it sounds logical to apply the same model for cognitive and behavioural problems of epilepsy (Table 2), much remains unknown regarding the contribution of shared versus syndrome-specific variables and clinical evidence suggests that especially behavioural problems do not necessarily respect such boundaries.

Mood and anxiety disorders

Mood and anxiety disorders are the most frequently reported psychiatric problems with prevalence rates up to 50% in selected popu-

Table 1. Prevalence of psychiatric disorders in unselected samples.

Psychiatric disorder	General population % (95%CI)	Epilepsy % (95%CI)
Any mental health disorder (lifetime)	20.7 (19.5–20.7)	35.5 (25.9–44.0)
Any mental health disorder (12 month)	10.9 (10.4–11.3)	23.5 (15.8–31.2)
Mood disorder (Lifetime)	13.2 (12.7–13.7)	24.4 (16.0–32.8)
Mood disorder (12 month)	5.2 (4.9–5.5)	14.1 (7.0–21.1)
Anxiety disorder (Lifetime)	11.2 (10.8–11.7)	22.8 (14.8–30.9)
Anxiety disorder (12 month)	4.6 (4.3–4.9)	12.8 (6.0–19.7)
Mood and anxiety disorder (12 month)	8.0 (7.6–8.5)	19.9 (12.3–27.4)
Suicidal ideation (lifetime)	13.3 (12.8–13.8)	25.0 (17.4–32.5)

Table 2. Cognitive and psychiatric problems in specific epilepsy syndromes (modified from (3)).

	TLE	FLE	BECTS	JME
Pathophysiology	Hippocampus and amygdala	Frontal lobe	Sylvian/Rolandic regions	Frontothalamic network
Cognitive problems	Memory	Executive functions	Language functions	Executive functions
Psychiatric problems	Mood and anxiety	Dyscontrol/ impulsivity	Unknown	Dyscontrol/ impulsivity

TLE= temporal lobe epilepsy; FLE= frontal lobe epilepsy; BECTS= benign epilepsy with centrotemporal spikes; JME=juvenile myoclonic epilepsy

Table 3. Clinical characteristics of psychoses in relation to seizure activity.

	Interictal	Ictal	Post-ictal	Alternative
Proportion among all psychotic episodes	~20%	~10%	~60%	~10%
Consciousness	Normal	Impaired	Impaired or normal	Normal
Typical features	Preserved personality, warm affect, lack of negative symptoms	Mild motor symptoms	Lucid interval, florid psychomotor excitation, mystic delusions	Subtle initial symptom (e.g. insomnia)
Duration	Months	Hours to days	Days to weeks	Weeks
EEG	Unchanged	Status epilepticus	Increased slowing	Normal/Improved

lations, such as tertiary referral centres or surgery programmes.[1,3] Mood and anxiety problems were historically attributed due to the number of social limitations (e.g. driving licence, job opportunities etc.), discrimination and stigmatisation even today connected with a diagnosis of epilepsy.[7] It is now evident that there is a solid neurobiological ground linking epilepsy to mood disorders such as the involvement of the mesiotemporal structures (hippocampus and amygdala) and the modulation of major neurotransmitter pathways (especially serotonin) by the epilepsy process and the antiepileptic drug treatment. Nonetheless, mood disorders are still unrecognised and untreated due to multiple reasons: i) lack of time during busy clinics, ii) lack of specific training by the treating neurologist in recognising mood disorders, iii) reluctance of the patient in acknowledging mental health issues. In addition, psychiatrists may also fail to diagnose mood disorders in epilepsy due to the high frequency of atypical clinical presentations, not fulfilling DSM or ICD criteria for a major depressive episode. In fact, up to 50% of patients with epilepsy and depression present with symptoms which are not considered diagnostic[8] because they are either too short in duration or they come in isolation. This notion has been eloquently discussed by Dietrich Blumer when he described the interictal dysphoric disorder (IDD).[9] The concept of IDD goes back to the original observations of Kraepelin and Bleuler, who described a pleomorphic pattern of depressive symptoms, intermixed with euphoric moods, irritability, fear and anxiety in patients with untreated epilepsy. Although the concept of IDD still remains controversial,[10] it is clearly evident that, for example, looking for typical biological symptoms of depression (e.g. insomnia or hypersomnia, reduced or increased appetite, sexual dysfunction etc.) is of limited value in patients with epilepsy as these symptoms can be influenced by the underlying disorder or the antiepileptic drug treatment. In addition, patients may often present with isolated or atypical symptoms (e.g. irritable/unstable moods, somatic symptoms) that are part of a mood disorder, deserving clinical attention and proper management even if it does not fulfil a categorical diagnosis. Recent research focused on screening instruments specifically developed for patients with epilepsy in order to overcome most of these problems. The Neurological Depression Inventory of Epilepsy (NDDIE) is an example.[11] In this context, it is easy to understand why suicide in epilepsy is still underestimated. Suicide represents, in the general population, the 11th cause of death, the 2nd in the group aged 25 to 34 years, but the overall risk is about three times higher in patients with epilepsy.[3] A number of studies tried to clarify potential reasons for that and there is still an on-going debate about the potential role of antiepileptic drugs. Many years after the Food and Drug Administration (FDA) issued the alert on a potential increased risk of suicide ideation and behaviour in people with epilepsy treated with AEDs, it seems now evident that the FDA warning was based on data affected by a number of methodological limitations.[12] Suicide in epilepsy is likely to be multifactorial in origin with biological, constitutional and psychosocial factors implicated, but specific programmes for screening and prevention are urgently needed.

Table 4. Seizure incidence during FDA regulatory clinical trials

Antidepressant drugs	%
Bupropion IR	0.6
Citalopram	0.3
Fluoxetine	0.2
Venlafaxine	0.1
Bupropion SR	0.1
Paroxetine	0.07
Nefazodone	0.04
Mirtazapine	0.04
Escitalopram	0.0
Duloxetine	0.0
Sertraline	0.0
Antipsychotic drugs	
Clozapine	3.5
Olanzapine	0.9
Questiapine	0.8
Ziprasidone	0.5
Aripiprazole	0.4
Risperidone	0.3

Psychoses and thought disorders

Although definitely less common than mood disorders, psychoses still represent a serious complication in patients with epilepsy affecting management and long-term prognosis. Prevalence rates for any thought disorder can be up to 4% in epilepsy, especially in hospital case series.[3] Psychoses of epilepsy (POE) have fascinated neuropsychiatrists for decades. They are conveniently classified according to their temporal relationship with seizures as peri-ictal or inter-ictal. Peri-ictal psychotic symptoms are more frequent than interictal ones with post-ictal psychoses (PIP), being probably the most frequently described (Table 3). PIPs are precipitated by a cluster of convulsions and are characterised by a period of normal mental state of 24-48 hours, also known as the lucid interval.[13] The pathophysiology of PIP is still unknown but seems to be related to that of the epilepsy. In fact, it is a highly stereotyped phenomenon, occurring mainly in patients with temporal lobe epilepsy and extra-temporal structural lesions.[14] Although PIPs are often characterised by spontaneous remission within days or weeks, antipsychotic drug treatment is required to reduce mortality and morbidity. In fact, the phenomenology of PIPs is characterised by aggressive behaviour and a florid psychomotor excitation often accompanied by a mystic delusion.[14] Chronic interictal psychoses (IIPs) represent nowadays a rare complication and the general impression is that this is probably due to a better and timely treatment of the epilepsy. IIPs usually develop subtly after many years of active lesional temporal lobe epilepsy due to, for example, hamartomas and gangliogliomas or other gross abnormalities.[15] If IIPs seem to occur less frequently than before, post-surgery psychoses represent a coming complication. Some patients are probably at increased risk and this is due to a specific neuropathological process not entirely elucidated.[16] The early identification of patients at risk during the pre-surgical assessment clearly deserves future research.

Finally, it is important to mention the Landolt's phenomenon, also known as "forced normalisation" or "paradoxical normalisation".[17] Originally described as an electrophysiological phenomenon associated with a particular class of antiepileptic drugs, namely

suximides, subsequent case series described a similar clinical pattern with all antiepileptic drugs, clearly pointing out that it is not drug-specific. In addition, recent case series reported the forced normalisation phenomenon in patients treated with vagus nerve stimulation and possibly after surgery. The pathophysiology is still obscure but it seems evident that, in some patients, the neurobiological mechanisms underlying seizure control antagonise normal thought processes. As already mentioned for psychoses after surgery, it will be important to identify specific biomarkers in order to recognise patients at increased risk.

The use of psychotropic medications in epilepsy

Data on treatment of psychiatric disorders in epilepsy are still limited and based mainly on clinical observations but during recent years, the International League Against Epilepsy has published a number of recommendations that represent a good reference for clinicians.[18,19] In general terms, internationally accepted guidelines for treatment of psychiatric disorders outside epilepsy should be adopted, taking into account all peculiarities of this special group of patients such as drug interactions and the potential effect of some drugs on seizure threshold.

New generations of both antidepressants and antipsychotics can be considered reasonably safe in patients with epilepsy, if appropriately prescribed in terms of titration and dosages. Among antidepressants, maprotiline, high dose of clomipramine and amitriptyline (>200mg), high doses of bupropion immediate release formulation (>450mg) may represent a concern. Among all antipsychotics, clozapine is the only one associated with a significant increased risk of seizures.[20] However, it is important to point out that available data comes from psychiatric samples (Table 4) and there is no data about seizure worsening in patients with epilepsy that are on a stable anticonvulsant regime. For this reason, any a priori assumption that psychotropic medications (even those just mentioned) are contraindicated in epilepsy is not based on any scientific evidence. The "start low/go slow" statement should always represent a starting point, bearing in mind that low starting doses do not necessarily correspond to low target doses and full remission from psychiatric symptoms has to be the primary goal of any psychopharmacological intervention.

Psychiatric disorders in epilepsy necessarily need to be approached by a multidisciplinary team because multiple skills and inputs from different specialists are needed. Still, true psychiatric symptoms should be distinguished from seizure-based behavioural manifestations in order to develop tailored treatment strategies. Continued clinical research and education are needed to grasp further insights into the fascinating relationship among epilepsy, seizures and behaviour and to provide the best care for patients with epilepsy.

Take home messages

- The new definition of epilepsy implies not only an enduring predisposition to generate seizures, but also its neurobiological, cognitive, psychological and social consequences.
- Epilepsy care need to be approached by a multidisciplinary team.
- The first goal in the treatment of any psychiatric problem in epilepsy should be full remission.
- Guidelines for treatment of psychiatric disorders outside epilepsy should be adopted taking into account individual patient needs, drug-drug interactions and risk of seizure relapse.
- Any psychotropic drug should be slowly introduced and slowly titrated according to clinical response bearing in mind that low starting doses do NOT necessarily mean low target doses.

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Non-invasive direct current brain stimulation for depression:

the evidence behind the hype

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Summary

- There is a major need for novel therapies in depression. One that has been suggested is transcranial direct current stimulation (tDCS), a form of mild, non-invasive electrical brain stimulation
- tDCS has been used effectively as an intervention for major depression, both alone and as an augmentative therapy combined with antidepressant medication
- Few studies have explored the neural mechanisms underlying the putative antidepressant effect of tDCS
- An improved understanding of the mechanisms underlying the antidepressant effect of tDCS is vital for enhancing clinical efficacy and predicting response to treatment, but this technique shows great potential as a safe, effective, and cost-effective therapy

The leading global cause of disability is major depression, affecting over 350 million people worldwide.[1] Pharmacological and psychological therapies for depression have changed very little in the past thirty years, despite extensive research for new treatment targets. The most common antidepressant drugs are effective for about 58% of depressed patients in primary care, while 45% respond to placebo.[2] The difficulty in developing new treatments arises in part because depression is a disorder of unknown aetiology. The neurobiological correlates of depression, on the other hand, are not entirely unknown: neuroscience research has identified several brain circuits that operate abnormally in depression. Recently, this knowledge has contributed to the development of experimental treatments, including those that stimulate the brain directly in a targeted manner. Among these novel treatments is a form of painless, noninvasive brain stimulation termed transcranial direct current stimulation (tDCS), commonly applied to the dorsolateral prefrontal cortex (DLPFC) in trials for depression. The practical advantages of tDCS are many: tDCS is comparatively inexpensive, portable, and safe. In this article we discuss the evidence that tDCS is effective in depression, and the neural and cognitive mechanisms that may drive its putative antidepressant effect. We also outline the importance of mechanistic studies of DLPFC tDCS to clarify its effects on the brain, and optimise its potential for clinical use.

What does tDCS do?

The use of weak electrical currents to stimulate the brain is not new, with reports dating back to the early 19th century.[3] Mild brain stimulation such as tDCS has benefited from recent computational modelling and neuroimaging studies aimed at refining stimulation parameters, including electrode size, current amplitudes, location and durations of stimulation.[4] tDCS uses a weak electric current to stimulate a localised area of the brain ('direct' indicates that the current flows in a single direction, in contrast to 'alternating' current stimulation). In early literature it was simply termed "polarisation", referring to its effects on neuronal resting potentials.[5]

Recent depression trials place the anodal electrode over the left DLPFC, with the cathodal electrode used as a 'ground' electrode, for instance supraorbitally. In this specific example, this creates an electrical circuit with current travelling from the anodal (positive) to the cathodal (negative) electrode. This delivers low levels of electrical stimulation through the skull immediately under the anode, typically between 1 and 2 milliamps, with a small proportion of that affecting the cortex beneath, facilitating (but not directly evoking) neuronal activity in part through its effects on the resting potential (see below). Although the entire physiological effect is likely more complex, this general potentiation of activity has been reported to produce marked behavioural effects in domains as varied as motor tasks, auditory learning, and language.[6] It is because of different electrode montages—electrode placement and current amplitude—that this technology can claim to modulate such an improbably diverse set of cognitive processes, including those involved in depression.

Table 1: Summary of key studies investigating the basis of tDCS as a treatment for MDD. RCT: Randomised controlled trial, HAM-D: Hamilton Rating Scale-Depression, BDI: Beck Depression Inventory, EEG: electroencephalography.

Study	Key finding	Limitations
Fregni[8]	• Pilot RCT: 5-session tDCS induced significant decreases in HAM-D and BDI	• Very small sample size (N = 10)
Loo[9]	• Large RCT: modest effect of tDCS after 3 weeks daily stimulation • Effect strengthened after 6 weeks	• All patients on stable antidepressant medication
Brunoni[10]	• RCT: combined tDCS + antidepressant medication more effective than either therapy alone	• No cognitive/neural correlates
Shiozawa[11]	• Meta-analysis: active tDCS statistically superior to sham in depression trials • Effect sizes vary somewhat between studies	• Low number of trials • Results specific to short term effects (no long-term trials)
Powell[14]	• EEG study: tDCS induces changes over medial frontal cortex during working memory performance • Extends understanding of tDCS neurophysiology to MDD	• Single session • Small sample size (N=18)

Why target the DLPFC?

One of the most established neural correlates of depression is abnormal metabolism in the DLPFC. Resting-state studies (e.g. using positron emission tomography: PET) tend to find a reduction in DLPFC activity in depressed patients, which normalises somewhat following symptom remission; by contrast, task-related activation (e.g. during working memory) is generally increased in the DLPFC in depression.[7] Lesion studies also support the hypothesis of DLPFC dysfunction in depression: patients with lesions involving the DLPFC show higher levels of depression than patients with lesions sparing the DLPFC.[7]

Increased task-related DLPFC neural activation is often interpreted as cortical inefficiency. While the primary role of the DLPFC is in so-called 'executive' function and cognitive control, it also plays a central role in emotion regulation, particularly in the reappraisal and suppression of negative emotions.[7] Thus, targeting the DLPFC with tDCS aims to remedy inefficiency in emotion regulation that could be central to depressive symptoms.

Clinical trials of tDCS in depression

The first double-blind, sham-controlled clinical trial of tDCS for depression reported very pronounced effects of tDCS on mood symptoms[8] following a relatively short stimulation period. Differences between active and sham (placebo) tDCS even persisted over the succeeding month.

Less marked (but nonetheless substantial) effects of tDCS were later reported in a three-week trial: tDCS improved mood significantly more than sham, but no difference between active and sham was found in response rates.[9] Cognitive effects were also smaller than reported in previous trials, with attention and working memory improvements found after the first tDCS session, but no (expected) cumulative cognitive enhancements independent of mood effects. More recently, a clinical trial found tDCS and sertraline to have comparable effects, but combined tDCS-sertraline treatment was more effective than either treatment alone.[10] However, null results have also been reported, and some studies find substantially larger effect sizes than others (see Figure 1).[11]

Differences in stimulation parameters, outcome measures, and timing of tDCS delivery could all account for variation in tDCS effectiveness. In the next few years, clinical trials should clarify the optimal schedule for tDCS intervention in depression (typically trials have administered stimulation five times per week), and only after this can large-scale trials determine whether it should be offered as an alternative treatment option. Very few serious side effects have been reported in any tDCS trials for depression, with the most common including temporary itching, tingling, or skin redness, and very limited reports of hypomania.[9,10] Thus, tDCS has great potential as a novel, safe, effective treatment for depression, but this can be realised only if the specific mechanisms and optimal stimulation parameters can be identified.[4]

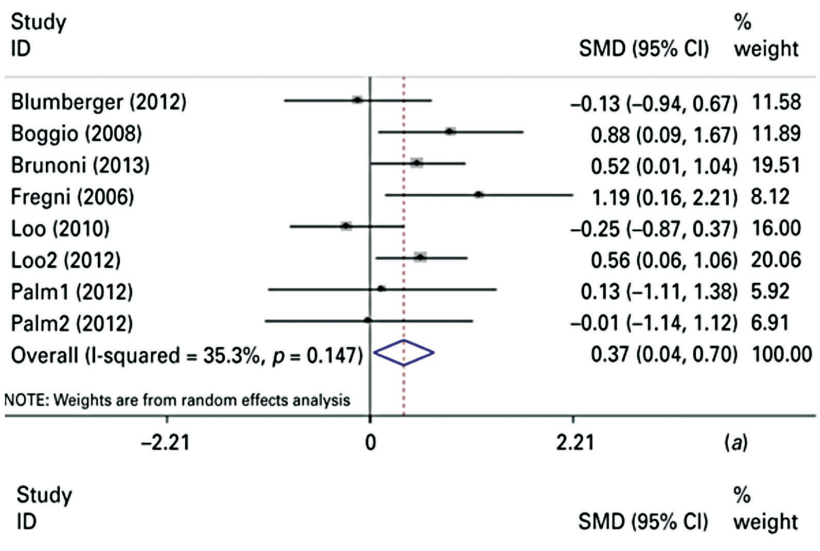

Figure 1.
Forest plot of effect sizes (Hedges' g) to illustrate the relative strength of treatment effects for each selected study, including the overall effect (vertical dotted line), the standardised mean difference (SMD), and confidence interval (CI). Figure reproduced with permission from Shiozawa et al, Int J Neuropsychopharmacol. 2014:11;1–10.

Discovering the mechanisms of tDCS in depression

Advances in the clinical development of tDCS will be boosted by improved understanding of the neurophysiological mechanisms underlying its behavioural effects. tDCS has polarity-specific effects on neuronal membrane potential: anodal tDCS decreases the resting membrane potential of the neuronal soma, increasing the likelihood of depolarisation, whereas cathodal tDCS raises the membrane potential of the soma towards hyperpolarisation[12] (see Figure 2). More widespread neural changes (i.e. away from the stimulation site), and local non-neuronal effects have also been reported, including local changes in ionic concentrations, levels of cyclic adenosine monophosphate (cAMP), protein synthesis, and NMDA receptor efficacy.[4,6]

Unfortunately for the purposes of understanding the effect of tDCS in depression, the neurophysiological mechanisms of tDCS have been studied predominantly in the motor cortex. The mechanisms driving 'antidepressant' tDCS over the DLPFC are poorly understood, though most studies corroborate the simple anodal-excitatory/cathodal-inhibitory model (though note that mild anodal currents can sometimes inhibit neuronal activity[13]).

One study investigating the neurophysiology of DLPFC tDCS found a polarity-specific effect on both working memory performance and EEG measures: anodal tDCS increased both behavioural performance and its electrophysiological correlates, while cathodal stimulation decreased both measures.[6] In currently-depressed patients, tDCS was reported to induce neurophysiological changes extending over the medial frontal cortex during working memory performance.[14] These studies provide insight into the role of the DLPFC in depression, indicating that tDCS might alter DLPFC efficiency as well as its interaction with more widespread prefrontal regions, driving the resulting behavioural and mood changes.

To date, most research on tDCS for depression has adopted one of two strategies: trials to determine whether tDCS improves depressive symptoms; or experimental studies, usually in healthy subjects, to determine its mechanism of effect. This division inhibits a better understanding of the specific mechanisms driving the antidepressant effects of tDCS. Studies combining both strategies have the ability to resolve this, and determine how tDCS could best target symptoms of depression.

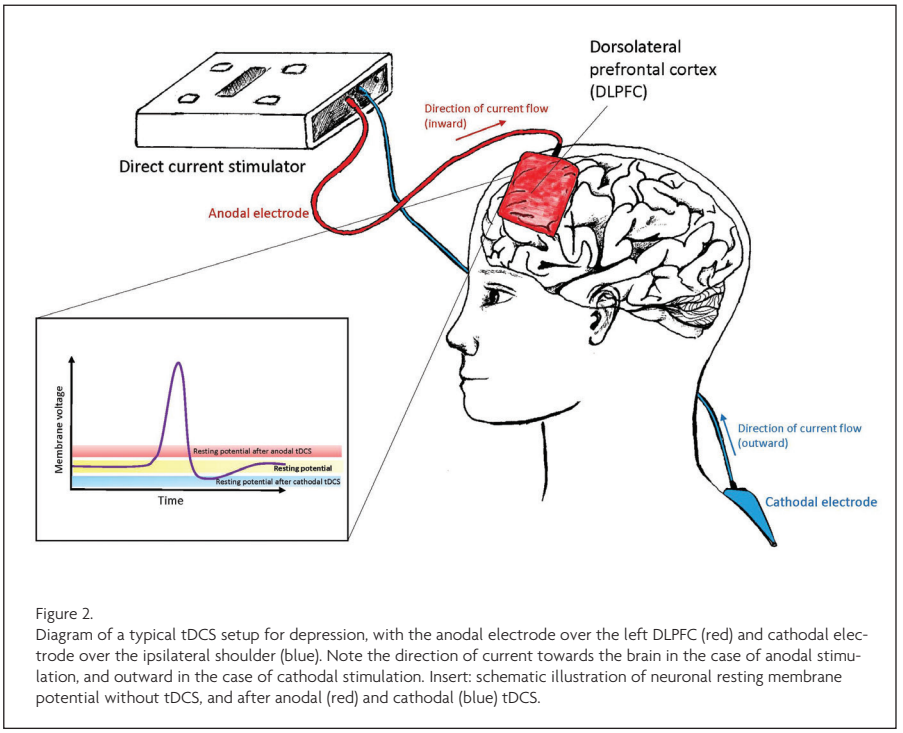

Figure 2.
Diagram of a typical tDCS setup for depression, with the anodal electrode over the left DLPFC (red) and cathodal electrode over the ipsilateral shoulder (blue). Note the direction of current towards the brain in the case of anodal stimulation, and outward in the case of cathodal stimulation. Insert: schematic illustration of neuronal resting membrane potential without tDCS, and after anodal (red) and cathodal (blue) tDCS.

Proceed cautiously—but not too cautiously

The most well-known electrical therapy in psychiatry is electroconvulsive therapy (ECT). Although evidence strongly indicates that ECT is an effective short-term treatment for depression,[15] it is perceived negatively by the public and its therapeutic efficacy is often tempered by concerns about cognitive side-effects. In the case of tDCS, which uses stimulation currents that are orders of magnitude lower than ECT, initial reports of cognitive enhancement with tDCS reignited public interest in electrical current stimulation. From these reports emerged an online community of 'home kit' tDCS users who report finding amazing effects, sometimes far beyond what has been shown experimentally. Within the neuroscience community, researchers have begun to question the magnitude of the reported benefits of tDCS.[16] An improved understanding of its mechanisms and effects is key to resolving these debates.

The challenge for basic and translational tDCS researchers is to convince clinicians that it is a credible experimental treatment, with the caveat that understanding its mechanisms will no doubt involve many more years of cellular, neurophysiological, and cognitive research. Putting treatment before mechanism is common in psychiatry: the neural mechanisms of proven effective treatments—cognitive therapy, electroconvulsive therapy, and many psychiatric drugs—are still relatively poorly understood. Still, history need not dictate future treatment discovery, and the tools of neuroscience can illuminate the biological and behavioural effects of tDCS alongside tests of its clinical efficacy. tDCS is only one of a number of experimental treatments for depression with origins in neuroscience, but it may hold particular potential as a new therapy, or as an augmentative strategy for existing therapies. The key will be honing the technology to target the complex and heterogenous nature of this debilitating disorder.

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Life after Neurosurgery

I've looked into the Abyss…

…And I have lived to tell the tale.

Patrick Williams
Patrick is currently training to be a Dentist. After being diagnosed with Trigeminal Neuralgia in early 2013, he became a member of TNA UK. He focuses his efforts on fundraising for the charity, as well as openly talking about the condition to raise awareness. He underwent Microvascular Decompression surgery in December of 2013 and has been in remission for over a year now. His aspiration is to become a General Dental Practitioner to be at the frontline of diagnosis to ensure no one suffers unnecessarily.

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Please note: An alias has been used to protect the identity of the author.

Trigeminal Neuralgia started as a tingle in my lip in early 2013, just after I turned 20. Never would I have thought that this tingle would turn into something that would be so wholly consuming; to the point where it seriously affected almost every aspect of my life, both physically and psychologically.

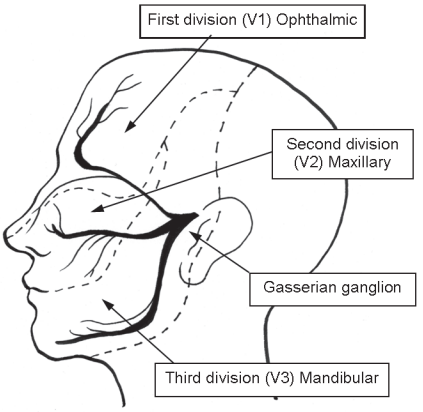
Two years later, I am in my final year of University, studying dentistry – a subject that I am incredibly passionate about. I'm often asked, 'Why dentistry?' It all stems back to when I was a small child and pulled out my own wobbly teeth, followed by pulling out my little sister's wobbly teeth too! As you can see, I was a gory little monster!

Back on topic, initially the tingles were only felt when I washed my face. Now, when I say tingle, it was more a "sharpness". It wasn't exactly pain…but it wasn't pleasant. Imagine if you'd bitten into a lemon and the sharpness made you withdraw. It was kind of like that, but along my upper left lip. I must admit, as a dental student studying many rare conditions, I was armed with far too much knowledge which sometimes made me occasionally neurotic! I instantly said: "This is Trigeminal Neuralgia". I lived with other dental students and told them of my suspected self-diagnosis. They all reassured me it certainly wasn't. I went to a medical professional with my concern, who also reassured me it certainly wasn't. A week or so went by, oh, it certainly was Trigeminal Neuralgia.

The pain was something that should be restricted to the most horrific and dire nightmares. Permit me to paint the picture. Imagine a knife that has been plugged into the main's electricity and repeatedly stabbing you, ripping from the lip to the teeth and up to the lower part of the eye and base of the ear. A microsecond pause. Then repeat, and repeat, and repeat…This electrically charged stabbing pain was relentless, repeating all day, everyday.

I eventually coerced my GP to write me a referral letter to a Neurologist. After a month of agony, I was seen by a specialist who confirmed my diagnosis. The drug regimes began. My world, which had already been turned upside down, was plunged down into the darkest place I have ever ventured. My life narrowed to existing, not living. Taking each second as it came.

I tried several drugs…and then combinations of drugs…and then drugs to control the side effects of the original drugs. Carbamazepine, oxcarbazepine, lamotrigine, gabapentin, pregabalin – I tried them all: a connoisseur of anticonvulsants. But all with little avail. The pain broke through the medical barrier in regular bursts, hundreds of times a day. 'Tic Douloureux' – painful tics in French – is an accurate name for this condition. The flinching was so bad I was once asked to leave a restaurant because the proprietor was worried about accidental damage and me knocking something over. I felt I was at battle with my body. The simple act of shaving turned into a task filled with dread. Even trying to eat soup through a straw become a fearful exercise. The drugs turned me into a zombie. I found it exhausting just keeping my eyes open for a few seconds, so much so it required another eight hours sleep. To stand at the Abyss, the darkest place you could ever be, look over the edge and truly wonder if it'd be better there than here. It is no coincidence that Trigeminal Neuralgia coined the term Suicide Disease.



On December 16th, 2013, Mr Ian Sabin, consultant neurosurgeon, performed a Microvascular Decompression (MVD) and returned me to a pain-free life. I was overjoyed. I came off my drugs slowly. There were a few tingles and a couple of sharp bouts. This terrified me. But Mr Sabin reassured me this was quite normal and would settle down. And it did. I am eternally grateful for what Mr Sabin did for me.

So where does Post Traumatic Stress Disorder fit into all of this? It's a condition that affects war veterans and those who have experienced the most terrible of things that are violently traumatic, right? So why was I there reliving hell? I would sit at my desk, ready to revise, so grateful for being alive and pain-free. But intrusive thoughts and images would invade my mind. What if it comes back? I suffered constant flashbacks of the worst situations I'd previously been in...like sobbing uncontrollably in public and getting odd looks or angry stares. Several times a week I would awake in a cold sweat imagining I'd felt pain in my face. I'd rub my lip viciously to confirm there was no pain...or was there? No, no, there was none, was there? Did I feel something just then? Had that been a tingle? If I drank

cold water and dental sensitivity occurred, I would be inwardly petrified. I couldn't focus. I developed 'safety behaviours' like double tapping wood or my head in order to not 'tempt fate'. The anxiety and incessant head tapping often brought on headaches, and I'd get sudden panic attacks which would stop me in my tracks, whether I was walking in the street or in clinic, making me feel as though I was about to be violently unwell.

I felt ashamed. There were people who had gone through far worse than me – wars and assaults. And there I was, a twenty-year-old with absolutely nothing wrong with him, having these intrusive thoughts just because of a condition that most people had never heard of. I was a freak.

I went back to my GP who rolled his eyes, but did agree to refer me to a therapist at Compass Wellbeing in London. After nearly a year of EMDR (Eye Movement Desensitisation and Reprocessing therapy) and CBT (Cognitive Behaviour Therapy) I came to understand it was irrational to feel this way. I was dealing with an uncontrollable stress response due to previous constant pain, fear, anxiety over when the next attack would be, or if I would stay pain-free now I was finally in remission. All these irrational thought processes had stacked up and never been dealt with. My brain had put these old memories and anxieties into boxes with open lids, so they spilled out whenever and wherever.

PTSD really impacted on my life. I wasn't able to form meaningful relationships with the people around me as I was so scared that no one would understand me, or that I'd be labelled as "some crazy" who considered himself a survivor of an imaginary disease! It wasn't only my social life that was affected. I was anxious all the time. I jumped at loud noises or unexpected movements. I had panic attacks at the most inopportune of times.

I believe Trigeminal Neuralgia really does impact on you mentally as well as physically. There needs to be a pathway for patients to get the emotional and mental support truly required. Not everyone will need or want it, but it should nonetheless be offered. It takes a lot of courage to ask for help, even more so to ask for mental health assistance because there is a stigma attached to mental health. Sometimes, all we need is for someone to acknowledge that what we're feeling is normal. That we're not freaks. We're Survivors.

So here I am, now aged twenty-two and life is sweet: Nearly two years in remission from Trigeminal Neuralgia; recovered from PTSD; a Trustee to a wonderful charity; a great social life; in my final year of dentistry and, possibly most important of all, now able to talk and write about my experience with Trigeminal Neuralgia and Post Traumatic Stress Disorder. Some days I may wobble, but I am not alone. I'm stronger now thanks to the cards fate dealt me and am proud of the path I walked.

A Tale of Two Taus

Reviewer: Dr Ed Needham, Neurology Registrar, Norfolk and Norwich University Hospital.

It is always exciting when a breakthrough in fundamental science leads to a concept that may be applicable to a wide number of diseases, and such is the case in the paper by Kondo et al., which primarily investigates the role of phosphorylated tau proteins (P-tau) in neurodegeneration following traumatic brain injury (TBI).

It has long been recognised that victims of TBI can develop a tauopathy known as Chronic Traumatic Encephalopathy (CTE), which bears a pathological semblance to Alzheimer's disease (AD). Furthermore, TBI is a risk factor for the development of AD in its own right. Despite clear clinical association, however, the pathophysiological bridge from TBI to CTE to AD remains elusive.

Previous work in AD has suggested that *trans* P-tau is a beneficial, physiological protein, whereas *cis* P-tau plays a pathogenic role in tauopathy (Nakamura et al., 2012). The authors of the current study developed monoclonal antibodies to both the *cis* and *trans* isomers of P-tau, and utilised them firstly to delineate the role of tau following TBI, hypoxia and metabolic stress, and secondly as therapeutic agents.

The paper starts with the identification of *cis* P-tau in the axons of all post-mortem brains from 16 patients with Chronic Traumatic Encephalopathy (CTE) compared with no patients in a control cohort of 8; the presence and distribution of trans P-tau was identical in both groups.

Murine models were then adopted to explore the temporal and spatial progression of tauopathy, and its subsequent effect on neurons. At 48 hours post-TBI, *cis* P-tau was detectable in a severity-dependent manner, and remained raised in those with both repetitive minor and single severe TBI. At this early time point the *cis* P-tau was restricted mainly to the cortex, but by six months the pathogenic tau isomer was detectable in other regions, including the hippocampi.

Identical production of *cis* P-tau was also demonstrated in two other models of brain injury: hypoxia and serum starvation.

To assess the pathogenic effect of *cis* P-tau on healthy neurons, the authors exposed cultured neurons to the brain lysate of TBI and healthy mice, and showed that *cis* (but not *trans*) P-tau was subsequently detectable in the neurons treated with TBI lysate, and was associated with accelerated apoptosis.

Having successfully utilised the mAbs to delineate the relative roles of tau in the above situations, attention is turned to their potential therapeutic value. Importantly, the *cis* P-tau mAb is highly specific in its binding, thereby avoiding unintended effects on the beneficial *trans* P-Tau, and universally beneficial effects of its application were seen in the various murine experiments. Immunodepletion of *cis* P-tau: prevented apoptosis in cultured neurons following the addition of brain lysate from TBI, hypoxia and serum starvation mice; stopped the spread of *cis* P-Tau from the cortex to other structures; potently inhibited the destructive processes affecting axonal microtubules and mitochondria; halted the development of tau oligomers, aggregation and tangle epitopes, as well as cortical and white matter atrophy; and protected against risk-taking behaviour (a putative consequence of medial prefrontal cortex damage) which was widespread in untreated TBI mice.

This study provides new insights into a therapeutically modifiable pathway which may have clinically significant implications in a spectrum of neurological disease states including primary neurodegenerative disorders, cerebrovascular disease, traumatic brain injury and hypoxic-ischaemic encephalopathy.

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A reappraisal of apomorphine

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Summary

- The highly potent dopamine agonist apomorphine is the only drug whose antiparkinsonian efficacy equals that of levodopa.
- When given as single SC injection, it leads to motor improvement within minutes and provides the most rapid and reliable relief from OFF symptoms currently available.
- When administered as continuous SC infusion, apomorphine enables a reduction in oral drugs and, in keeping with the concept of continuous drug delivery, may lead to marked improvements in patients with motor complications that have become refractory to adaptations of oral and transdermal treatments.
- As the least invasive among the device-aided treatments, apomorphine should be considered in all patients with refractory motor fluctuations that have a negative impact on patients´ quality of life.

Dopaminergic replacement therapies typically improve motor problems in Parkinson´s disease (PD). Over the disease course, however, the response to levodopa doses becomes shorter and patients become aware of the recurrence of their parkinsonian symptoms at the end of the dose effect. The management of these motor fluctuations may be relatively straightforward while OFF periods are limited to end-of-dose effects and while gastrointestinal absorption remains reliable.[1] However, OFF periods may become refractory, and they may be associated with highly unpleasant non-motor symptoms.[2] Frequently, it is the emergence of involuntary movements associated with ON periods that makes management of motor fluctuations complex and further reduces quality of life.[3] Although our understanding of the mechanisms underlying motor complications remains incomplete, the short half-life of oral antiparkinsonian drugs such as levodopa is involved. Oscillations in plasma and synaptic dopamine concentrations are believed to induce maladaptive changes in basal ganglia motor circuits.[1,4] This concept has been supported by animal studies and findings in PD patients, where the longer-acting dopamine agonists as initial treatment (instead of levodopa) can delay the onset of motor complications,[5] while motor complications can be ameliorated by switching from short-acting oral drugs to the continuous application of the same drugs.

Infusion therapies that provide stable drug delivery are available for patients whose motor complications have become refractory to all adjustments to the oral medication. Both levodopa and apomorphine infusion have fewer contraindications than deep brain stimulation and therefore represent an option for a broader spectrum of patients. While intrajejunal levodopa infusion requires the insertion of a tube through the abdominal wall, apomorphine is administered subcutaneously. It is thus the least invasive and the most easily reversible of the device-aided treatments.

Apomorphine

Apomorphine is a non-ergot dopamine agonist which stands out among the dopamine agonists in several ways: It is the only drug with an effect on parkinsonian motor signs equal to that of levodopa. Due to its low bioavailability, it must be administered parenterally, usually subcutaneously. When injected, the drug leads to the most rapid relief from parkinsonian motor problems currently achievable with any drug.

The substance has been known since the 19th century and was in use for psychiatric and veterinary applications but only infrequently for PD symptoms. As the long-term complications associated with levodopa were recognised, apomorphine was investigated further and was re-introduced into clinical use in the UK, by Professor Andrew Lees and his team at UCL. Starting from this long tradition in the UK, it is now also licensed in many other countries, both as intermittent injection therapy and as SC infusion. Alternative modes of delivery have been explored and a sublingual formulation is being investigated further.

Injection therapy

Following a SC injection, the effect sets in after 5-20 (mean 7) minutes and lasts for around 40-60 minutes. Many open, uncontrolled studies of apomorphine injections as an add-on to oral treatment showed a mean reduction of daily OFF time by around 50% compared to baseline.[6]

Several randomised, placebo-controlled studies confirmed this effect.[7,8] Importantly, using this treatment, motor improvement can be achieved in a very reliable manner, once each patient's individually required dose has been established: A randomised study demonstrated that 95% of OFF periods were terminated by apomorphine, compared to 23% on placebo. As expected with a short-acting drug, ON time with troublesome dyskinesia also increased, although not significantly.[7]

This treatment is suitable for patients with refractory or troublesome OFF periods which persist despite optimised oral and transdermal treatment. Patients must be able to distinguish

between OFF symptoms and other problems such as dyskinesia, and must be able to handle the injection device during an OFF phase; or must have a carer able to do so. The injections are usually administered using a pen, with the individually optimised dose pre-set.

Patients with troublesome dyskinesia during ON periods are less good candidates and all patients should be observed with regards to worsening or new onset of dykinesia.

Practical approach

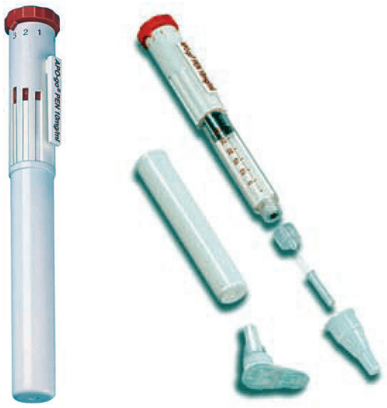
To determine the individual dose, patients undergo a challenge test. This can be done on an out-patient basis, if required. Domperidone, a peripheral dopamine receptor blocker, is used for one to three days before starting apomorphine to avoid nausea. Domperidone has been linked to QT prolongations and in 2014, the European Medicines Agency limited the daily dose to 30mg and stated that the drug should not normally be used for longer than one week.[9] Alternatively, trimethobenzamide may be used. A study of ondansetrone (without placebo arm) showed less efficacy than domperidone, albeit in untreated patients.[10]

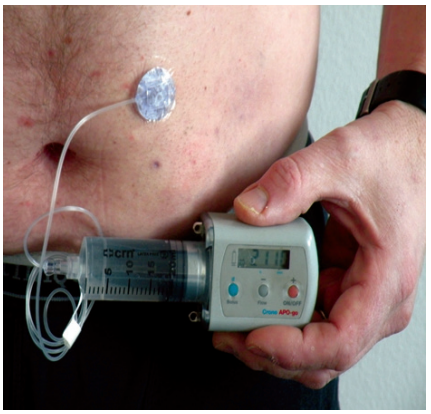
Starting during an OFF period, increasing doses of apomorphine are injected until a full ON is achieved (or until intolerable, adverse side effects occur) and the patient is observed for motor response as well as tolerability. The first dose is usually 1 or 1.5mg, with increments of 1 or 1.5mg every 30-45 minutes, but more rapid titration schemes are also used.[11]

Continuous infusion therapy

Several uncontrolled studies showed marked reductions in daily OFF time from baseline when apomorphine is administered via continuous subcutaneous infusion during waking hours. The largest, retrospective, study was multi-centre and reported a reduction in daily OFF time by 4.3 hours.[6] Randomised comparisons with other treatments have not been performed but a European placebo-controlled multi-centre study is on-going (*Toledo Study*).

Some uncontrolled studies also reported reductions in dyskinesia severity, by 34% up to 83%. One study using levodopa and apomorphine challenge tests before and six months after initiating apomorphine infusion showed a reduction in dyskinesia severity by 34-44% on blinded video ratings.[12] Maximum dyskinesia improvement has been observed after several months.[13] Dyskinesia reduction may be more marked in patients who manage to substantially reduce their oral therapy, and consequently, the mean daily apomorphine doses in studies reporting effects on dyskinesia have been in the range of 100 mg.[13] "Apomorphine monotherapy" has been defined as infusion only during the waking day with discontinuation of oral drugs, except in the morning and at night.[12,13,14] The determinant factor for dyskinesia reduction is likely





the overall reduction of short-acting agents,[1] and strict monotherapy is not necessarily required, particularly when the problem is refractory OFFs rather than dyskinesia. The observed improvement in motor complications is in keeping with the current concept and believed to be due to the replacement of pulsatile with continuous drug delivery.

There is some evidence suggesting relevant improvements in non-motor problems. A non-randomised study found a significant improvement in the overall score of the Non Motor Symptom Assessment Scale for PD (NMSS), from 106 (SD 65) to 56 (45) points (p=0.0003), including in sleep, mood, perception, attention, urinary and gastrointestinal symptoms, and this was associated with a significant improvement in quality of life.[15]

Practical approach

In practical terms, infusion treatment is usually initiated on an in-patient basis although this is not an absolute requirement if frequent visits are possible and increases in the flow rate are done slowly.[16] An apomorphine challenge test is not required although some centres perform this to determine an approximate dose range that the patient will require. Tolerability cannot be judged sufficiently from a challenge test as slow increases in the hourly flow rate of the pump help to avoid adverse effects.

The pump is usually worn on a belt around the patient's waist and the needle is inserted into the abdominal skin into rotating injection sites. During the initial in-patient stay, patients and carers are instructed in handling the pump, including hygiene measures. Oral dopamine agonists are usually withdrawn completely during the initial in-patient stay, and subsequently other oral antiparkinsonian drugs are gradually reduced or withdrawn over weeks and sometimes a few months while the flow rate of apomorphine is increased. While the standard daily duration of infusion is around 14-18 hours, some patients with severe nocturnal OFFs benefit from 24-hour administration, with lower doses at night.

Safety

Potential adverse effects of apomorphine include dopaminergic effects including nausea, orthostatic hypotension, leg oedema, or somnolence.

Skin nodule formation is very common on infusion – although usually mild to moderate – but rarely problematic with injection therapy. Rarely, abscesses or ulcerations occur on infusion therapy. Widespread nodules may impair reliable and stable absorption of apomorphine. Local treatments include massages, application of corticoid creams, or silicone patches. Only therapeutic ultrasound has been investigated in a randomised study, with results suggesting efficacy. [17]

Haemolytic anaemia is rare (below 1%)[6] but regular screening is required. Coombs Test has been described to turn positive in 6-12.5% although this may be reversible. Haemolytic anaemia requires discontinuation of apomorphine and treatment in collaboration with haematology specialists.

Neuropsychiatric adverse effects may occur. As with other dopaminergic drugs, vulnerable patients may develop impulse control disorders but no comparative studies exist to show whether these are more common than with other dopamine agonists. Other neuropsychiatric problems are typically associated with long disease duration. These include punding, a behavioural disorder with repetitive, prolonged activities resembling normal recreational or domestic activities (e.g. cleaning, using a computer); and dopamine dysregulation syndrome, a drug dependency syndrome with craving for increasing dopaminergic doses despite detrimental behavioural changes and often dyskinesia, which also occurs on high doses of levodopa. It is unknown whether confusion or hallucinations are more common than with oral dopamine agonists but there is evidence suggesting relatively good neuropsychiatric tolerability of apomorphine: A small non-randomised study showed improvements in the cognitive / emotional categories of the NMSS over one year in the apomorphine group but not in the medically treated group.[15] Another non-randomised study found significant improvements in these categories in 43 patients on apomorphine infusion, with similar findings in patients on intrajejunal levodopa.[18] Several small studies in patients using apomor-

phine infusion while on waiting lists for DBS showed stable scores on the Neuropsychiatric Inventory over several years.[19] An uncontrolled multi-centre four-year study reported drop-outs due to neuropsychiatric adverse events in only 8 out of 166 patients.[6]

Technical problems rarely result in treatment discontinuation. Issues occasionally seen include clotting of connections, arrest of the pump, and disconnection of the syringe. Patients receive instructions on which oral / transdermal medication to use in case a technical problem cannot be dealt with immediately. Teams including a nurse with special interest in PD are best suited for the management of patients using infusion therapies for the motor complications of PD.

Choice of advanced PD treatment

The indication for SC apomorphine infusion is the same as for intrajejunal levodopa infusion and deep brain stimulation (DBS): motor complications which have become refractory to all adaptations of oral and transdermal treatments and which have a relevant impact on a patient's quality of life.

It is usually advisable to discuss device-aided treatments early when a patient's motor complications become difficult to manage, to reassure them that further options are available.[20] The choice of treatment is ultimately the patient's and the clinician must tell the patients and any caregivers which treatments are options for them (and why others are not). With all device-aided treatments, it is important to point out that the effect that can realistically be achieved is similar to each patient's individual best ON state but ideally with less dyskinesia and fewer medication-induced adverse effects. Therefore, many problems that persist during ON will likely not be resolved by infusion therapies. Examples include balance problems, freezing, dysarthria and dysphagia during ON.

Contraindications for infusion treatments are less strict than for DBS. The spectrum of patients who are potential candicates for infusion therapies is wider than for DBS, particularly because there is no age limit and because infusions may be tried in patients with mild cognitive impairment or mild dementia if adequate caregiver support is available. Similarly, balance problems and falls during ON are important contraindications for DBS but not for the infusions, although they are unlikely to improve.

Due to the lack of randomised studies comparing levodopa and apomorphine infusion, it is not known whether there is a difference in their efficacy on motor fluctuations and dyskinesia. Their adverse effect profiles and contraindications differ somewhat, however: Levodopa infusion may be complicated by local infections including peritonitis and by technical complications, and has been linked to an increased risk of polyneuropathy. In contrast, adverse effects typically associated with dopamine agonists are likely more common with apomorphine, such as nausea, daytime sleepiness, orthostatic dysregulation, oedema and neuropsychiatric changes. If these problems pre-exist in a patient, they are relative or absolute contraindications for apomorphine, depending on the severity. Marked dementia is a contraindication for apomorphine but not necessarily for levodopa infusion, provided adequate care-giver support exists. However, apomorphine has the advantage of being less invasive and more easily reversible than levodopa infusion, allowing a lower threshold for a treatment trial.

As such, apomorphine infusion should be considered in patients as soon as motor fluctuations are becoming difficult to manage and it is likely that many more patients could benefit from apomorphine if this option were considered for all potential patients.

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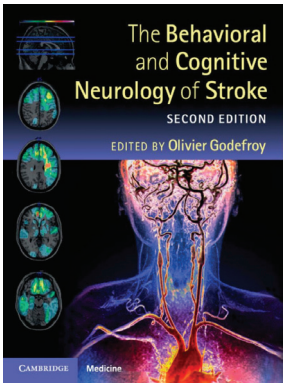
The Behavioural and Cognitive Neurology of Stroke

Edited by: Oliver Godefroy, 2nd Edition. **Published by:** Cambridge University Press. **ISBN:** 9781107015579. **Price:** £89.99. **Pages:** 464. **Reviewed by:** Dr Sumanjit Gill, Stroke Physician, UCL.



Behaviour and cognition form a fascinating aspect of Stroke Medicine. This has been extensively covered in a 32 chapter book edited by Oliver Godefroy, with contributions from more than fifty physicians, well respected in the field. The book explains and clarifies the cognitive sequelae of strokes, so often underestimated in clinical practice where screening assessments may be relied upon because of the unavailability of specialist Neuropsychology.

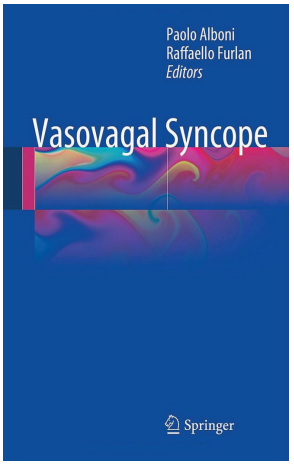
The problems are often unmasked as the patient attempts to reintegrate into everyday life after discharge. The difficulties may be raised in outpatient consultations, where the opportunity for detailed assessment may be even more limited than on the wards. More subtle deficits may not be evident until a patient tries to return to work; their ultimate consequences may be far from subtle. Taking the perspective of planning care and organising services, cognitive and behavioural problems have a huge impact on rehabilitation: at the most obvious level, inability to recall information about exercises between sessions can easily impede progress to motor recovery.

The book is divided into three sections which cover: vascular cognitive impairment; the 'analytic approach'; and, finally, dementia and management of vascular cognitive impairment. The largest is the middle section which contains 6 subsections and 26 chapters covering clinical syndromes such as alexia and agraphia, akinetic mutism and proposagnosia. Each chapter has key points to highlight the most relevant sections of text and plenty of illustrations/diagrams to help the reader follow. Each chapter is relatively short and easy to digest. Despite the number of authors, the text flows well from one to the next. Extensive referencing is provided.

This book as a whole is recommended for neurologists and non-neurologists dedicated to the field of Stroke Medicine and for generalists who encounter stroke patients in their clinical practice.

Vasovagal Syncope

Author: Alboni P, Furlan R (eds.). **Published by:** Springer. **ISBN:** 9783319091013. **Price:** £95.23. **Pages:** 326. **Reviewed by:** AJ Larner, Cognitive Function Clinic, WCNN, Liverpool.



Many referrals to neurological services are for episodes of transient loss of consciousness (TLoC), more often as a consequence of syncope than epileptic seizure. The neurological component of these events is reflected in terms such as "neurally-mediated syncope", "neurocardiogenic syncope", and "reflex syncope", but because the efferent limb of this reflex produces circulatory effects (cardio-inhibitory: bradycardia; and vasodepressor: hypotension) it often also falls to cardiologists to assess these patients. Few neurologists have an expressed interest in these conditions (this book clearly shows that syncope is no more a unitary condition than epileptic seizure). This may be because the division of the nervous system at fault is the autonomic branch, which, perhaps akin to stroke, has traditionally failed to draw many neurological recruits. Accordingly, although it clearly behoves neurologists to have some familiarity with syncope, it has largely been cardiologists who have driven the agenda in terms of research and guidelines. Since TLoC crosses professional clinical boundaries, one can see the point of dedicated "Syncope units".

This book, itself from a "Cardiology" series, contains chapters on syncope epidemiology, pathophysiology, clinical and diagnostic aspects, prognosis and treatment, as well as related topics, including the relationship to fibromyalgia, chronic fatigue syndrome, and postural orthostatic tachycardia syndrome (POTS), all of which may also feature in neurological practice (and may be associated with autonomic dysfunction).

Although typical syncope may be easily diagnosed on clinical grounds alone, atypical syncope presents significant challenges, sometimes requiring tilt-testing, an investigation absent from the menu at most neurological centres. There is no syncope biomarker, although B-type natriuretic peptides are being examined (there is no mention of co-peptin, despite a 2013 paper suggesting its potential utility). Implantable loop recorders have illuminated pathophysiology and provided indications for pacemaker insertion in some patients, but these obviously fall outwith the neurological remit.

Considering the differential diagnosis, I was initially surprised to see the inclusion of cataplexy (p31,174,282), but as many episodes of syncope in the elderly may present as "unexplained falls" with minimal or no prodromal symptoms and/or retrograde amnesia, this differential is logical. Cognitive testing is advocated in elderly patients with unexplained falls (p290). Syncope is often contrasted with epileptic seizure, but surprisingly there is no mention of NEAD as another differential, although this may overlap with "functional (psychogenic) pseudosyncope". The roles of non-pharmacological (e.g. counter pressure manoeuvres) and pharmacological treatments for syncope have little existing evidence base, of the latter the best evidence is probably for midodrine.

In my judgment, this book may be recommended to neurologists seeking a refresher or wanting to learn more about this topic. The contributors are mostly Italian (such is the enthusiasm that even Calgary is claimed to be in Italy! See p297), leading to some infelicities of language (persistent use of "associated to" irked me; "conclusive" for "concluding"). The absence of an index is a serious deficiency!

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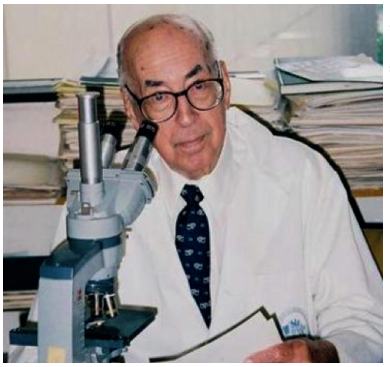
Foundations of Modern Stroke Medicine:

The legacy of C Miller Fisher

Dr Charles Miller Fisher (December 5, 1913 – April 14, 2012) developed and wrote about the key scientific ideas that underpin almost every aspect of modern stroke medicine. His insatiable curiosity and formidable scientific ability were applied to meticulously describe clinical and pathological features of many types of stroke. A major theme that Dr Fisher developed can be summed up as the idea that: "strokes do not occur at random", but instead follow characteristic patterns according to their cause and mechanism. He authored more than 200 publications detailing his observations.[1] Some of the most significant discoveries are listed in Table 1. Every stroke clinician will immediately recognise the impact these have had on both our conceptual understanding and daily clinical practice.[2] A single stroke unit ward round today might include the recognition of lacunar stroke syndromes, the urgent recognition and treatment of symptomatic carotid artery thrombo-embolism, and the diagnosis of a "late life migraine accompaniment" mimicking stroke or transient ischaemic attack (TIA).



C Miller Fisher

Life before becoming a physician held great challenges for Miller Fisher, which may have shaped his extraordinarily determined and productive career in stroke medicine. He was born in 1913 in Ontario, into a large family of eight siblings, and then studied medicine in Toronto, where he was awarded his degree in 1938. He joined the British Royal Navy at the outbreak of war and spent three and a half years interred in a German Prisoner of War Camp, after his boat, HMS Voltaire, was sunk off the coast of Cape Verde. He spent nine hours in the sea, waiting to be rescued, on the very day his wife was due to give birth to their first child, and – in typically uncomplaining manner – reportedly said: "I thought perhaps she was in more trouble than I was". He trained as a neuropathologist in Boston, and then returned to Montreal, where he began to define what he called "transient ischaemic attacks". In perhaps his most famous observation, he repeatedly noted "premonitory fleeting symptoms" (including limb sensory symptoms, and monocular visual loss) experienced by patients prior to a hemispheric ischaemic stroke, and made the crucial link to carotid artery atheromatous disease. This led to wide acceptance of the thrombo-embolic theory of ischaemic stroke and TIA. He then moved to Massachusetts General Hospital in the 1950s where he had a long and highly productive career, in the process creating the first stroke service. He died at the age of 98, in 2012, leaving two sons and a daughter.[1,3]

Table 1. Some of Miller Fisher's outstanding contributions to stroke medicine[2]

1. Thromboembolism as a stroke and transient ischaemic attack mechanism
2. Carotid artery disease and stroke
3. Characteristics and causes of TIA
4. Causes and treatments of atrial fibrillation related stroke
5. The lacunar hypothesis and stroke due to small vessel occlusion
6. Localisation of brainstem injury
7. Post subarachnoid haemorrhage vasospasm
8. Mechanism of haematoma growth in intracerebral haemorrhage
9. Reversible cerebral vasoconstriction syndrome
10. "Late life migraine accompaniments" and the associations between migraine and stroke

Table 2: Fisher's Rules: our personal pick
• Make the patient bedside your laboratory: study the patient seriously
• Settle an issue as it arises at the bedside: whenever possible, don't leave a "maybe"
• Always be working on one or more projects; it will make the daily routine more meaningful
• Always try as hard as you can to disprove your hypothesis before accepting it
• Describe quantitatively and precisely: the details are important
• Fully accept what you have read or heard only when you have verified it
• Write often and carefully. Let others gain from your work and ideas.
• Resist the temptation to place the patient into a diagnostic cubbyhole which fits poorly
• The patient is always doing the best they can. Be supportive and never be angry with a patient or their family.
• Maintain a lively interest in patients as people

Miller Fisher thrived on the intellectual challenge of clinical practice and became legendary for his dedicated care and teaching, which inspired generations of physicians who trained with him. Louis Caplan, one of his clinical fellows, captured this approach in "Fisher's Rules", which remain a blueprint for becoming a great stroke clinician and scientist. We have listed our personal pick, but urge you to read the full publication in order to better understand the attitudes and values he promoted (Table 2).[4]

Miller Fisher's ideal of lifelong learning through detailed observation was uniquely coupled with tremendous communication skills and empathy for the plight of patients affected by stroke. Descriptions abound of Miller Fisher in his office poring through his copious notes to correlate clinical observations with pathological findings. After his death his colleagues carefully collected these notes: one trainee doctor reportedly even checked through the bins to retrieve some that were accidentally disposed of!

One of the greatest lessons we can take from Miller Fisher's life is that he made every day's work an opportunity to make an observation or original contribution. "If you could describe that," he would tell the attendees of his weekly case conference, "if you could really describe that patient's findings and disease mechanism carefully and accurately, you would be the first to do so." While evidence based medicine in large populations is key to modern neurological practice (and especially to stroke medicine), Miller Fisher reminds us of the power of detailed narrative observations on the symptoms of disease and its impact in the individual patient. This is the way in which new patterns and mechanisms of disease are recognised, and by which the correct treatment for each patient can be determined through logical principles. Dr Miller Fisher (or CMF, to those who knew him) continued ward rounds until he was almost 90 years old, always asking the question "what can the patient teach us?" – a lesson which we would all do well to remember, even in this era of ever more sophisticated investigative techniques.

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1. Mohr JP, Caplan LR, Kistler JP. *In Memoriam: C Miller Fisher.* Stroke 2012;43:1739-40.
2. Greenberg SM. *C Miller Fisher: An Appreciation.* Stroke 2013;44:171-2.
3. Caplan LR, Mohr JP, Ackerman RH. In Memoriam: Charles Miller Fisher (1913-2012). Arch Neurol. 2012;69(9):1208-9. doi:10.1001/archneurol.2012.1743.
4. Caplan LR. *Fishers Rules.* Archives of Neurology. 1982;39:389-90.

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

2015 – November

Ketogenic Study Evening
9 November, 2015; Dublin, Ireland
Jacqui McAleer, E. jmassociates1@me.com

Examining the utility of music interventions in neurological disorders of older people
Monday 16 November, 2015; RSM London, UK
Lucy Church, T. 0207 290 3928, E. rsmprofessionals@rsm.ac.uk – www.rsm.ac.uk/livemusicnow

Modern Thinking in MS Management
7pm Friday 20 November - 16:40 Saturday 21 November, 2015; The Palace Hotel, Manchester, UK
www.modernthinkinginms.com

11th Essential Neuro MRI Course
Saturday 21st November, 2015; Liverpool Medical Institute, UK
One day intensive course in how to interpret MRI Brain & Spine – 6 Cat 1 CPD
Contact: Sam Pickup, T. 0151 709 9125 or E. essentialcourses@hotmail.com

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

Ketogenic Study Evening
25 November, 2015; Liverpool, UK. Jacqui McAleer, E. jmassociates1@me.com

The 2nd British Symposium on the History of Neurology and Psychiatry
A commemoration of the centenary of the death of Sir William Gowers
November 25th, 2015; Institute of Neurology, London, UK
Programme and registration details: Liz Beckmann at www.hnps.co.uk2016

History of Neurology and Psychiatry in London
November 26th, 2015; Institute of Neurology, Queen Square, London, UK
Programme and registration details: Liz Beckmann at www.hnps.co.uk2016

23rd Annual Meeting of the European Charcot Foundation
26-28 November, 2015; Milan, Italy – www.charcot-ms.org

December

The Brain Series: Sports and the brain
Evening of Thursday 3 December, 2015; RSM, London
Organised by: Clinical Neurosciences Section – www.rsm.ac.uk/events/cng02

Bipolar Disorder 2015
3 December, 2015; London, UK. T. 020 7501 6762, www.mahealthcareevents.co.uk

The Encephalitis Society Professional Seminar
7 December, 2015; London, UK
T. +44 (0)1653 692583, E. admin@encephalitis.info – www.encephalitis.info

BNPA Neurology & Psychiatry SpRs Teaching Weekend
11, 12 13 December, 2015; Oxford, UK. T.0560 438 3951, m. 07940 591096, E. admin@bnpa.org.uk

2016

January

London Sleep Medicine Training Course 2016
14 - 16 January, 2016; London, UK. T. 020 7501 6762, www.mahealthcareevents.co.uk

February

Dementia 2016
11-12 February, 2016; London, UK. T. 020 7501 6762, www.dementiasconference.com

Is it criminal? Acquired brain injury, challenging behaviour and rehabilitation
Partnerships in Care Brain Injury Services Conference 2016
24 February, 2016; Cambridge, UK
www.partnershipsincare.co.uk or contact samantha.coburn-kett@partnershipsincare.co.uk

March

Treating Depression 2016
24 March, 2016; London, UK. T. 020 7501 6762, www.mahealthcareevents.co.uk

Neurology 2016: leading edge neurology for the practising clinician
30th March - 1st April 2016; London, UK. T. 020 344 84460, E. Jean.reynolds@ucl.ac.uk

May

ABN Annual Meeting 2016
17-19 May, 2016; Brighton, UK. T. 020 7405 4060, E. info@abn.org.uk

Invited opinion piece:

NICE guidelines on delaying and preventing dementia in later life

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To cite:
Larner AJ. ACNR 2015;15(5):20

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1. Lincoln P, Fenton K, Alessi C et al. *The Blackfriars Consensus on brain health and dementia.* Lancet 2014;383:1805-6.
2. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. *Risk score for the prediction of dementia in 20 years among middle aged people: a longitudinal, population-based study.* Lancet Neurol 2006;5:735-41.

This recent production from NICE – full title "Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset. NICE guidelines [ng16] www.nice.org.uk/guidance/ng16 – was published in October 2015. Dementia prevention is thus part of a job lot, along with disability and frailty.

Essentially this is a public health document, produced by a Public Health Advisory Committee (PHAC), devoid of diagnostic considerations. It seems to be based largely around "evidence statements" from the Cambridge Institute of Public Health, where Professor Carol Brayne has a long standing interest in these issues.[1]

There are in all 15 recommendations delivered in two subsections: promoting healthy lifestyles (8) and service organisation and delivery (7). The headline recommendations are summarised as: stop smoking; be more physically active; reduce alcohol consumption; adopt a healthy diet; and achieve and/or maintain a healthy weight. Nothing objectionable there, you may think; but read on!

Colleagues (and relatives) have asked me, based on the publicity in the media garnered by the document, whether we really do have to stop drinking alcohol altogether. Section 4.19 states that "PHAC heard expert testimony suggesting that, in light of current evidence and issues with the evidence base, the overall message should be that there is no safe level of alcohol consumption". I presume that the "expert testimony" in question emanates from the erstwhile President of the RCP. The "issues with the evidence base" seem to revolve around the possibility that "non-drinkers", who fare worse than moderate drinkers (the J-shaped curve), are in fact mostly ex-heavy drinkers, hence the reason that non-drinkers do badly. I'm not sure whether this is evidence or opinion: if the former, a few apposite references would not have gone amiss to try to convince the populace of what may be seen as a Draconian measure.

Some economic modelling has been undertaken, and this apparently "estimates that the biggest gains in reducing dementia come from interventions that raise physical activity levels from sedentary to low level activity" (Section 4.34). The key public health message, though hardly novel, may therefore be "More exercise!".

As with previous NICE documents which I have read, this can hardly be described as a gripping encounter, unless you enjoy the deeply self-referential nature of NICE productions. It reads as a series of prescriptions and proscriptions for behaviour modification, an approach which might be described as managerial or "Skinnerian", since it seems largely uninterested in the cognitive processes which cause people to fail to adopt, or indeed to do the opposite of, what promotes health.

The emphasis on dementia prevention is, of course, welcome (likewise the recommendations for further research). The failure of current therapeutic approaches suggests that prevention really may be a more appropriate strategy than cure, and the mid-life risk factors for dementia are well-recognised.[2] But will this document have any impact, or deliver the desired effects? No one will ever know, because, as with all NICE documents which I have read, there is never any expectation or plan to measure impact.

[NB The opinions expressed here are those of the author, and do not necessarily represent those of his employers.]

PREVIEW: British Neuropsychiatry Association

Conference details: 11-12 February, 2016, London UK. ***Report by:*** BNPA President – Dr Alan Carson, Consultant Neuropsychiatrist, Western General Hospital, Edinburgh.

One of the highlights of being President is announcing the following year's British Neuropsychiatry Association's AGM.

The 2016 AGM will be held at the Royal College of Surgeons in London on 11th and 12th February. At the February 2015 meeting it was a particular pleasure to have so many neurologists and psychologists attending. The primary aim of the BNPA is to bring different professional groups together in order to enhance our knowledge and understanding of brain disorders and as a consequence improve the quality of care we give to our patients, so if you enjoyed last year, and you all seemed to, come again: and better still bring a friend or colleague along. The quality of meeting is dependent on the delegates!

In 2016 we will be taking a developmental perspective on adult disorders. The phrase 'funny-looking' is common occurrence in clinic. I feel sure I am looking at a neuro-developmental problem but I don't really know where to begin…all will be explained.

We have known for years that aversive experience in childhood can lead to depression in adults – but have you ever wondered what the mechanism is and importantly why some people are resilient and some are not? Can the risks of adversity be passed between generations? The epigenetics of depression may hold the answers.

Epilepsy used to be simple – we had generalised seizures that were presumed genetic and focal ones caused by a lesion. Not any more-there is an increasing awareness of genetic focal seizures. How do we approach this in clinic? Attention Deficit Hyperactivity Disorder and its management with Ritalin has been debated for years – but what are the effects on adults, and, more importantly, what should we be doing for adults with these complaints.

The afternoon will hear this year's JNNP lecture by Professor Francesca Happe on autism, the junior members' prize papers and research updates on novel therapeutics in epilepsy and sleep and psychiatric disorders.

The Friday will focus on language and its complexities. Thomas Bak will take us through a general introduction, outlining the structure and function of human language. Jonathan Schott will get us up to date with new understandings of primary progressive aphasia and what study of this group of degenerative disorders tells us about language. The term 'knights move thinking' seems to stick in every medical students mind but what actually is formal thought disorder in schizophrenia?

David Linden will explain the complexities of this understudied condition. The commonest language disorder most of us encounter is aphasia after stroke – but what we really want to know is what is its prognosis and what can we do to treat it?

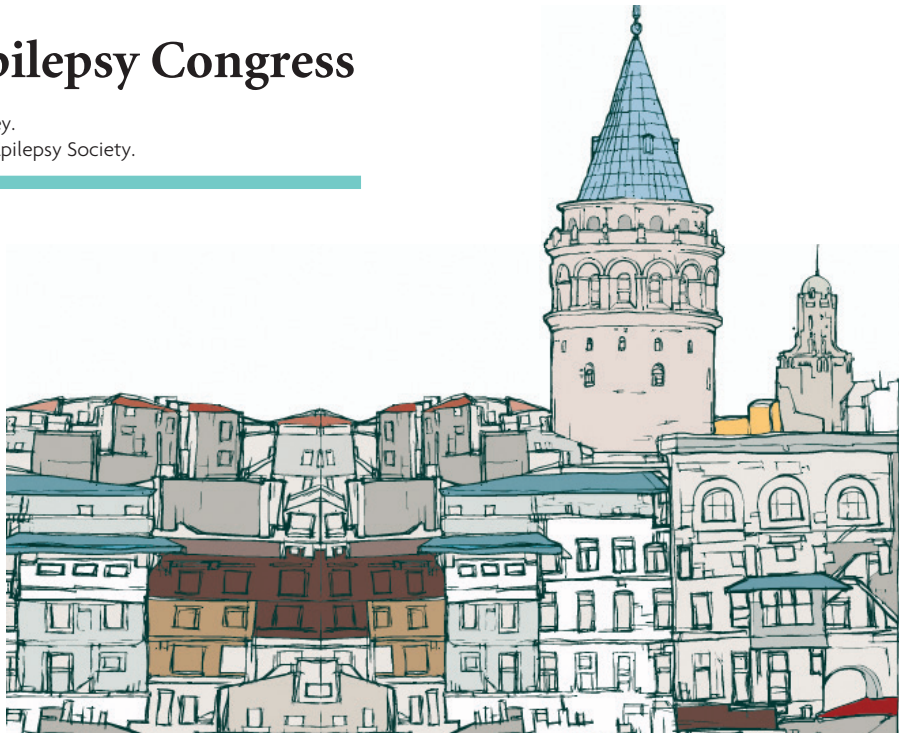
The 2016 BNPA medal will be awarded to Professor Chris Frith whose pioneering work in neuroscience will be known to many with his insights into the cognitive basis of schizophrenia, passivity phenomena, and delusions. He has currently started a new line of enquiry and his medal lecture "Co-operation and Consciousness" sounds fascinating.

The meeting will draw to a close with the BNPA debate; the Rev Professor Alasdair Coles and Professor Anil Seth will discuss 'Is there room in a modern concept of psyche for a soul and spirituality', but as ever at BNPA debates it is what you the delegates think that may offer most insights.

I hope you will share the sense of excitement that I, and my fellow directors, have for this programme and that we will see as many of you as possible in London.

31st International Epilepsy Congress

Conference details: 5-9 September, 2015, Istanbul, Turkey.
Report by: Nicola Swanborough, Publications Editor, Epilepsy Society.



Istanbul has long been recognised as a crossroads of culture, learning and trade. Its position on the ancient Silk Road made it historically significant in opening up communication channels between civilisations from as far afield as China, Africa, Arabia and Europe.

So it seemed fitting that the city should have been chosen as the location for the 31st International Epilepsy Congress (IEC) – the first major international epilepsy event to take place following the approval of the resolution of the Global Burden of Epilepsy by the World Health Assembly in May of 2015.

The resolution called for countries around the world to make epilepsy a priority. It called on healthcare professionals, lay stake holders and policymakers to improve epilepsy care, promote research and disseminate knowledge and understanding of the condition.

Istanbul's IEC, organised by the International League Against Epilepsy and the International Bureau for Epilepsy, ticked every pill box, a prescription for a rich interchange of hopes, frustrations, advances and question marks on an international platform.

Genetic research into epilepsy is presenting hope and frustration in equal measures. Professor Sanjay Sisodiya from University College London Institute of Neurology and director of clinical genetics at Epilepsy Society presented the case of a patient who spoke for the first time in 15 years after a genetic diagnosis revealed she had Dravet syndrome. Correct diagnosis led to a change in medication and enabled her to talk once again, often with a degree of wit.

'This illustrates the fact that even after a lifetime of severe epilepsy, it is still possible to regain a degree of cognitive performance,' he told delegates.

However he pointed out that understanding how a person's DNA may influence their response to different treatment options including anti-epileptic drugs, dietary therapies and surgery, was an area of research that was still lagging behind other areas.

'While ever people are having seizures and living with the consequences of seizures, we still have a job to do. We can and we should do better,' he said.

Neurologists from Switzerland, the US and Belgium reported that people with drug resistant epilepsy were often being denied the chance to benefit from treatments such as neurostimulation as governments refused to invest in therapies that initially could appear more costly.

Speaking at a symposium on drug resistant epilepsy, Professor Philippe Ryvlin from Switzerland said many people worldwide could benefit from treatments such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS), but governments were reluctant to invest in these therapies.

'There are many forms of neurostimulation that could offer a reduction in seizure frequency and severity for those with drug resistant epilepsy,' he told delegates, 'but it all comes down to cost effectiveness.'

James Wheless, neurologist from the US agreed: 'We all know that VNS, like epilepsy surgery, comes at a high cost, but ultimately it could save the system money. You have to pay up front and then save money further down the road.'

Epilepsy experts said while 70 percent of people with epilepsy should have their seizures controlled with medication, the reality was that only 52 percent were seizure free, leaving a treatment gap of 18 percent.

Chair of the symposium, Professor Paul Boon from Belgium, said: 'For those with drug resistant epilepsy, we must optimise their seizure control, minimise side effects and maximise quality of life. Treatment options such as neurostimulation exist for these people and could help to close the treatment gap.'

Delegates crowded into the main auditorium to hear Professor Helen Cross of Great Ormond Street Hospital, London, discuss the latest findings from the trials into the medicinal use of cannabis in the treatment of severe childhood epilepsy syndromes.

Professor Cross is the chief UK clinical investigator in the first UK trials of cannnabidiol, a component of cannabis which does not contain the psychoactive component THC. She had been asked to discuss whether cannabis was a miracle or a fairytale, but if delegates were hoping for a definitive answer, this was not the moment.

Cannabis is neither a miracle nor a fairytale, Professor Cross told her audience. In its pure form she said it could offer some benefit in treating epilepsy, but that benefit may be no greater than that offered by one of the new anti-epileptic drugs.

She continued: 'We have to be particularly concerned about the effects of the drug on the developing brain in children. It is vital that we carry out further long-term safety tests into cannabidiol so that we can ensure its tolerability, sustainability and efficacy.'

Professor Ley Sander from University College London Institute of Neurology and Medical Director of Epilepsy Society told delegates that the power of Google was now forcing healthcare professionals to be more open and informative with patients about Sudden Unexpected Death in Epilepsy (SUDEP).

He said that with so many people accessing information via Google, it was now imperative that healthcare professionals should discuss individual risks around SUDEP, so that the information could be put into context.

'SUDEP has always been an issue but with so many people looking up "Dr Google" and finding out about SUDEP themselves, it is important that as healthcare professionals, we address the issues in a sensitive and timely manner,' he said.

'More and more people are coming to clinic and starting the conversation themselves and this is a good opportunity to explain both about the rarity of SUDEP and also the importance of minimising individual risks.'

Professor Sander also stressed that SUDEP was not the only risk of premature mortality in epilepsy. He said that where a person's epilepsy was caused by an underlying illness such as a brain tumour or cardiovascular disease, their risk of premature mortality could increase.

'We need to better understand the interaction of these co-morbidities that are driving the rate of premature death. We also need to identify structural and genetic biomarkers that will alert us that an individual is at a greater risk of SUDEP.'

Faculty of Neuropsychiatry Annual Conference

Conference details: 10-11 September, 2015, Royal College of Psychiatrists, London, UK. ***Report by:*** Dr George El-Nimr, Academic Secretary for the Faculty of Neuropsychiatry and Clinical Lead of Neuropsychiatry Services in North Staffordshire. ***Conflict of interest statement:*** The author declares that there are no conflicts of interest.

With over 360 delegates from all over the country and other countries (including Australia, Singapore, Canada, Pakistan, Netherlands, New Zealand, Belgium, Sweden and Czech Republic), the Faculty's Annual Meeting was a great success. This oversubscribed event was held at the recently acquired new headquarters of the Royal College of Psychiatrists in London and has indeed received excellent feedback. The programme covered a number of clinical management, medico-legal and service delivery issues that were discussed in the form of key note talks and a selection of seminars. A number of eminent clinicians, barristers and academic speakers along with the support received from service users, have certainly contributed to the success of the conference. This event highlighted the real meaning of families, scientists and clinicians working together in enhancing research, education and clinical care. A senior psychiatrist who is also a former patient with brain injury discussed his rocky journey, surviving a significant brain injury and being able to resume clinical practice and also contribute to medical education. It was particularly inspiring to hear about specific neuropsychological symptoms from someone who is able to articulately describe these and give a first-hand experience of what they mean.

Following introductions from Dr Rafey Faruqui, Faculty Chair and Dr George El-Nimr, Academic Secretary, Professor Nick Fox discussed the role of neuroimaging in the management of dementia of the working age. Professor Fox discussed how this field is now moving away from a purely exclusionary approach towards the use of imaging as a positive predictive diagnostic tool. Professor Fox has also made reference to functional imaging and recent developments in molecular imaging. Within the same theme of neurodegenerative conditions, Dr Ed Wild has presented recent research data and research developments that do provide hope along the difficult journey of hunting for a cure for Huntington's disease. Furthermore, Dr Wild discussed how working with pre-manifest mutant gene carriers can provide a model that could potentially be adopted in studying other neurodegenerative conditions.

A subsequent session was dedicated to discuss Neuropsychiatry on the frontline. Professor George Tadros has argued the case for psychiatrists to work more readily within an acute hospital setting. Arguably, this would not only improve mental health care for our patients but is also more appreciated by colleagues who work in acute medical and surgical settings. The positive financial impact

of that approach was discussed and highlighted by the RAID model that is adopted in a number of mental health trusts. Similarly, Dr Alex Ball has presented a case for integration of Neuro-rehabilitation and Neuropsychiatry. Nonetheless, the importance of maintaining specialism was argued to be of particular relevance to patients with acquired brain injury.

A session entitled "The Mind on the Operating Table" explored the history of psychiatric neurosurgery in the mid-20th Century which was eloquently presented by Dr Ken Barrett. Professor Marwan Hariz followed that talk discussing current practices of neurosurgery for mental disorders.

A session under the heading of "The Brain on the Move" discussed the coexistence of psychiatric morbidity in patients with movement disorders. The concept of motion and emotion was discussed in details by Professor Andrea Cavanna. A specific talk on the treatment challenges of Tourette's syndrome was presented by Dr Davide Martino who highlighted the importance of appreciating the role of psychological interventions along with pharmacological treatments, presenting an update on current evidence.

The event was also able to address a number of medico-legal dilemmas; enhancing the understanding of the interaction between the legal system and care services. Relevant topics were explored by eminent presenters form both camps. In addition to key note talks about the uses and abuses of the law in brain injury by Professor Mike Barnes and assessing capacity for the Court of the Protection by Ms Jess Flanagan, Barrister, some of those issues were also discussed in the form of seminars that invited further audience participation. A highly educational and interesting session was presented in the form of a mock trial where pre-prepared court reports were presented and senior clinicians were cross-examined by barristers from opponent parties.

Conference delegates were also able to join various other seminars. These covered a number of clinical topics including movement disorders and social cognition, Parkinson's disease: beyond motor features, Neuropsychiatric aspects of alcohol misuse, epilepsy and behaviour and brain injury service models.

With a selection of poster and oral presentations, trainees were able to present a number of high quality projects to the conference delegates. Prizes were given to the best poster and oral presentations at the end of the second day of the conference.

The conference programme included a business meeting where members were invited to discuss important training and national issues related to neuropsychiatry. The success of this year's conference was highlighted and discussions have been held in relation to ideas for next year's conference that is scheduled to take place on the 15th and 16th September 2016 at the Royal College of Psychiatrists in London.

Key messages:

- The value of Neuroimaging in dementia goes beyond excluding alternative diagnoses.
- Considerable advances have been achieved in studying potential disease modifying treatments in Huntington's disease.
- There is a case for Neuropsychiatry to have a stronger presence in the general hospital.
- Mental Health professionals should arguably be more involved in shaping the future of Neurosurgical practices for severe mental illness.

EAN/WSO/AAN/IBRO/WFN/EHF/LINF 7th Regional Teaching Course (RTC) on Neurology in Sub-Saharan Africa

Conference details: 15-17 October, 2015, Khartoum, Sudan. ***Report by:*** Professor Peter Sandercock, MA, DM, FRCPE, FMedSci, Professor of Medical Neurology and Honorary Consultant Neurologist, University of Edinburgh, Professor Erich Schmutzhard, MD, DTM&H(Liv.), Professor of Neurology and Critical Care Medicine, University Innsbruck, Austria and Chair, EAN Task Force Neurology and Africa and Eveline Sipido, EAN Liaison Officer.

The 7th RTC took place in Khartoum, Sudan and was hosted by the University of Khartoum. The RTC, organised by the EAN, was supported by a consortium of European and international scientific societies:

- University of Khartoum, Sudan
- PAANS – Pan African Association of Neurological Sciences
- WFN - World Federation of Neurology
- AAN - American Academy of Neurology
- IBRO - International Brain Research Organisation
- EHF – European Headache Foundation
- WSO - World Stroke Organisation
- LINF Lundbeck International Neuroscience Foundation

An unrestricted educational grant was also obtained from the Lundbeck International Neuroscience Foundation. Our gratitude goes to the local organising team led by Osheik Seidi. His help and the support of the University of Khartoum and the Faculty of Medicine at the University was essential for the success of the RTC.

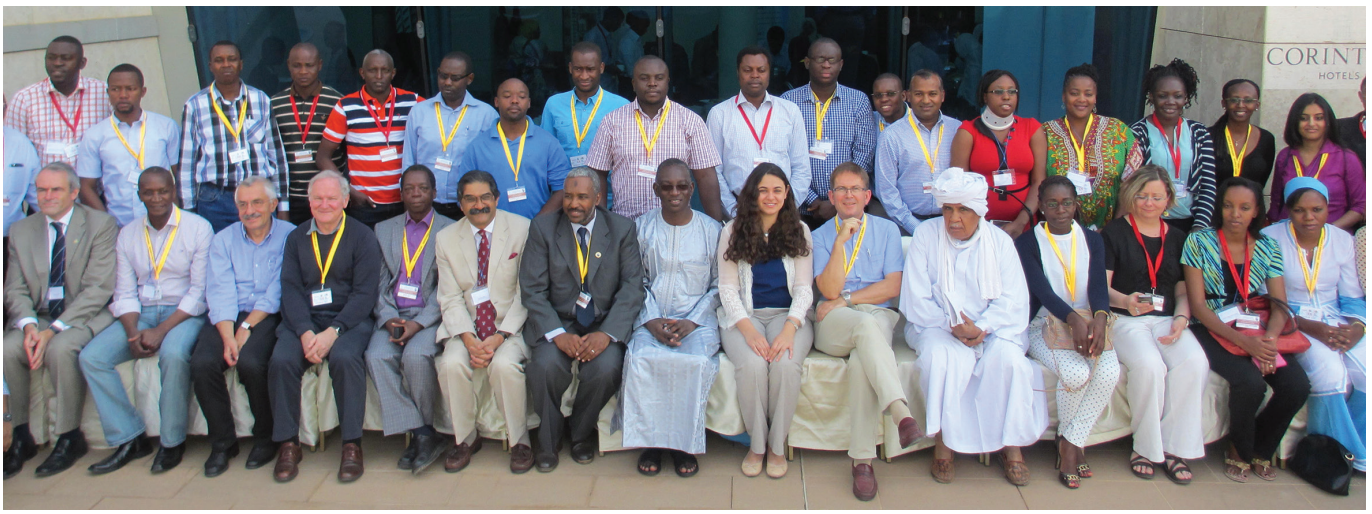
Thanks to the support of these societies, 33 young doctors and trainees coming from 19 SSA countries could be invited to the 7th RTC and were supported by a scholarship from the RTC fund. These individuals were selected and put forward by their Head of Department as potential course participants. Thus these selected participants represent some of the very best trainees from across Africa. Many doctors and trainees from the University of Sudan as well as other medical training centres attended the course and the RTC counted 123 registered participants representing 20 SSA countries. The Faculty for the course was also truly international and its members represented 13 different countries. This three-day RTC had two main themes: stroke and neuro-paediatrics.

Professor Osheik Seidi (2nd from Left) local organiser, at the opening ceremony at the Ministry of Education.

RTC Faculty and the scholarship students

Faculty: Osheik Seidi (Sudan), Erich Schmutzhard (Austria), Riadh Gouider (Tunisia), Amadou Gallo Diop (Senegal), Peter Sandercock (UK), Jose Ferro (Portugal), Raj Kalaria (UK), Farrah Mateen (USA), Marieke Dekker (Tanzania), Charles Newton (Kenya), Richard Idro (Uganda), Tim Lynch (Ireland), Alvin Ndondo (South Africa), Hannah Cock (UK). Case presenters Anne Pita Lomole (South Sudan), Yohannes Debebe (Ethiopa), Ziryab Imad Mahmoud (Sudan).

The core organisation of the course is led by the EAN Task Force "Neurology and Africa" chaired by Prof Erich Schmutzhard (Austria)



RTC Faculty and the scholarship students

Erich Schmutzhard (Austria) discussing a case of cryptococosis.

Marieke Dekker discussing a case of Myasthenia Gravis.

together with Mrs Eveline Sipido, EAN Liaison Officer and responsible for overall organisation of the RTC. The high international reputation for academic excellence of the course is underlined by the wide range of learned societies and institutions that support this annual course. Also the support received from major regional institutions such as the Sudanese Ministry of Higher Education and the University of Khartoum, underline the importance of the event within Africa.

The format of the course was a mixture of lectures in the morning, supplemented by a case presentation fitting into the theme of the day. The case presenters were: Dr Yohannes Debebe (Ethiopia), Dr Anne Pita Lomole (South Sudan) and Dr Zyriab Imad Mahmoud (Sudan).

The afternoons were taken up with small group interactive workshops to discuss cases brought by the experts; these rotating sessions were intensive, but proved particularly popular with the participants (and enjoyable for the Faculty!). The trainees brought a great many questions that arose from their daily practice; this unique opportunity for them to ask the Faculty questions and to network with their peers from across the continent was something they really valued. There was also a formal "Meet the Professor" Session that was very much appreciated. Hannah Cock introduced all to the EAN's eBrain on-line learning resource, which will be made available to all HINARI countries free of charge.

An evening session hosted by the Faculty of Medicine of the University of Khartoum and dedicated to the analysis of video presented clinical cases was lead by Timothy Lynch, Hannah Cock and Riadh Gouider. This open session saw the participation of an impressive number of medical students.

It was a real privilege to attend the course as a teacher and to learn from the clinical and scientific expertise of the faculty in the sessions and in the discussions. While the international faculty might bring knowledge of recent scientific advances to the table, the regional faculty brought their extremely rich clinical experience and wisdom in how to apply that knowledge in the diverse health care systems of Africa. Likewise, the trainees very much appreciated this unique opportunity for them to ask the Faculty questions and to network with their peers from across the continent.

The meeting was organised to a very high standard, and clearly meets the need to build capacity in caring for people with neurological disorders in the African continent, where the burden of disease related to both communicable and non-communicable diseases of the nervous system is high; stroke in adults and – in children – epilepsy and infections being disorders with a high burden of disease in the region.

To meet this continuing need, the EAN-led planning group met in Khartoum to plan the next course. The participants to the 7th RTC were asked to list up to three topics of interest they would like to see addressed in a future RTC. From the compilation of the topics received, two that had the highest request were identified for the 2016 RTC. July 14th – 16th 2016 and the main themes will be 1) Spinal cord diseases, 2) Neurodegenerative diseases (including post stroke cognitive decline and dementia), 3) Emerging and vanishing infections of the nervous system in SSA. Prof Jean Kaboré, University of Ouagadougou, will be the local host of the 8th RTC.

Given the very large numbers of questions I fielded about stroke over the course of the RTC, I have no doubt that the support from WSO will prove to have been an extremely cost-effective investment that will help develop a cadre of stroke neurologists in Africa to tackle the emerging epidemic of NCDs there. Finally, the generous gift of one year's free membership of the WSO to all course participants was very warmly received.

You Tube videos from the course

All videos
https://www.youtube.com/user/EpilepsySociety/videos?sort=dd&view=0&shelf_id=2

Professor Ley Sander from University College London Institute of Neurology and medical director of Epilepsy Society, on the importance of epilepsy research
https://www.youtube.com/watch?v=bsgT61lRR-U

Professor Ley Sander from University College London Institute of Neurology and medical director of Epilepsy Society talks about the risks of SUDEP
https://www.youtube.com/watch?v=bsgT61lRR-U

Professor Sanjay Sisodiya from University College London Institute of Neurology and director of clinical genetics at Epilepsy Society explains how genetic diagnosis enabled a woman speak for the first time in 16 years
https://www.youtube.com/watch?v=u-e7xye8CgY

Epilepsy Society's neuropsychologist Sallie Baxendale discusses epilepsy surgery outcomes
https://www.youtube.com/watch?v=jbJSufnGX9Q

Professor Helen Cross from Great Ormond Street talks about cannabis-based drugs and epilepsy
https://www.youtube.com/watch?v=p00SOeT9ddk

Brain surgeon Andrew McEvoy discusses smart technology and epilepsy
https://www.youtube.com/watch?v=nDROrhXoBo8

Professor Matthew Walker from University College London discusses pioneering gene therapy and epilepsy
https://www.youtube.com/watch?v=JqrU1Xxrk_0

Evaluation by MS Trust reveals vital MS services face critical challenges

Vital NHS services that people living with MS rely on are facing increasing pressures which could lead to inequities in care, according to a major new report published by the MS Trust.

Evidence for MS specialist services, the findings from the MS Trust's three-year GEMSS evaluation project, provides an unprecedented insight into the state of MS services, at a crucial moment in their development. Collecting data from 15 MS teams who provide services for over 15,000 people living with MS, it demonstrates the vital service that MS specialist nurses provide, the value they deliver and highlights the challenges they face in providing care.

The report reveals that people with MS rely on their MS specialist nurse for expert knowledge, support and continuing, co-ordinated care, and are more likely to turn to them than any other health professional – including neurologists and GPs. Without them, people with MS say they would have to manage alone, or seek care from overstretched GPs or even A&E departments without specialist knowledge and experience – at an increasing cost to the NHS.

The data reveals that more and more of MS specialist nurses' time is required to support people taking disease modifying drugs – and the MS Trust is aware of growing pressure to increase the UK's comparatively low treatment rates. However, half of the people living with MS in the UK have progressive forms of the disease and are not eligible for these treatments. They have complex and challenging care needs, but with the greater focus on drug management, there are concerns that it will be increasingly difficult to deliver an equitable service for everyone with MS.

The report also reveals that people with MS are finding it hard to access MS education and symptom management courses because of the pressures on specialist nurses' time and resources. This training can help people living with MS manage difficult symptoms such as fatigue, pain, bladder and bowel problems, visual disturbances and mobility problems.

"We know from the feedback we receive every day that MS specialist nurses provide an incredible service to over 100,000 people living with MS in the UK," said Amy Bowen, Director of Service Development at the MS Trust. "This report gives us the strongest evidence yet into the exact value of the care they provide. With new approaches to MS being developed and new treatments becoming available, we believe MS specialists nurses are going to become even more important in ensuring co-ordinated care for everyone living with MS. Following the success of this project, the MS Trust will continue to work closely with MS services to help them meet the needs of everyone living with MS."

With its new MS Forward View project beginning in 2016, the MS Trust plans to work with MS nurses, neurologists, allied health professionals, pharmacists and other MS experts to show how MS services can provide greater access to care, making best use of current resources and skills, and still deliver value to the NHS.

New toolkit to help provide better health services for people with epilepsy

Two leading epilepsy charities have joined forces and created a web-based toolkit for commissioners which will provide all the information required to ensure high quality services for the 500,000 people living with epilepsy in England.

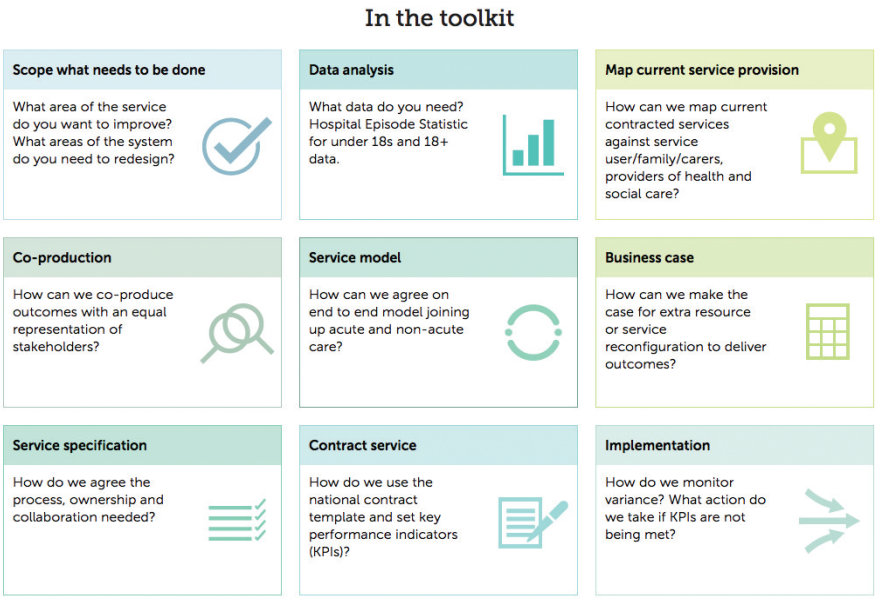
Epilepsy Action and Epilepsy Society identified the need for the commissioning tool after a survey of Clinical Commissioning Groups (CCGs) in 2014 identified gaps in planning. Epilepsy Action contacted 211 clinical commissioning groups. 204 responded and of these 78% stated that they had not produced, and had no plans to develop a written needs assessment of the health and social care needs for people with epilepsy.

The two charities therefore decided to develop the web-based hub, the 'Epilepsy Commissioning Toolkit'. It has been developed and tested with the support of a group of nine CCGs who have a range of experience in commissioning epilepsy services.

The project has gained RCGP and the Association of British Neurologists endorsement and is going through the NICE endorsement process and is being championed by NHS England National Clinical Director for Adult Neurological Conditions, Dr David Bateman.

The toolkit has been organised into nine sections giving practical examples based on experience such as calculating local populations of people living with epilepsy, reading examples of service models, creating business cases and more.

A key area will be Hospital Episode Statistics (HES) data from the Public Health England Neurology Intelligence Network including numbers of unplanned admissions for epilepsy, neurology outpatient usage and benchmarking with other CCGs.



Epilepsy Society's Juliet Ashton, the first national nurse consultant for epilepsy and part of the development group, said: "For the last 18 months, I have been working closely with CCGs across the country reviewing services for people living with epilepsy and, working alongside Peri O'Connor from Epilepsy Action, we've carried out rigorous testing of the Epilepsy Commissioning Toolkit to ensure the content is fit for purpose."

Dr David Bateman said: "This is an excellent example of how the voluntary sector and commissioners can work together to benefit patients. Epilepsy is a common condition but is often difficult to treat and without the correct care pathways can be an economic burden to the NHS. There are many forms of information, tools and data which exist for epilepsy, however these can be a challenge to find and require some knowledge of what is available. This project has pulled together information and templates to develop best value services to support adults and children with epilepsy."

www.epilepsytoolkit.org.uk

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Dr Charles Alessi

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Professor Mark Baker

Imaging in dementia
Professor John O'Brien

Age-related brain changes
Professor Klaus Ebmeier

Hospital liaison
Professor George Tadros

Psychological therapies for people with dementia and their carers
Reinhard Guss

Safe discharge of people with dementia from acute hospitals
Dr Andrew Teodorczuk

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Alzheimer's disease treatment targets: an update
Professor Roy Jones

Person centred dementia care
Professor Dawn Brooker

End of life care
Dr Liz Sampson

Understanding functional ability in dementia
Dr Iracema Leroi

Delirium
Dr Elizabeth Teale

Update on legal aspects of dementia
Dr Jonathan Waite

Global action on dementia
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