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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

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SPOT SPMS is a medical educational campaign which was created and funded by
Novartis Pharmaceuticals UK Ltd and is intended for UK healthcare professionals only.

THE LONGER THE WAIT THE MORE DAMAGE IT CAUSES[1-3]

1 in 2 people with RRMS will progress to SPMS within 20 years.[4] Mary may only be 39, but she's been experiencing difficulty finding words and slower thinking. These cognitive symptoms can be a sign of SPMS.[5,6] And its damage can be irreversible, making an early diagnosis essential.[1,7]

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UK | March 2022 | 196257 RRMS=relapsing remitting MS; SPMS=secondary progressive MS

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Todd Hardy, Co-Editor.

The latest issue of ACNR begins with an article from Heather Angus-Leppan and colleagues from London who have developed an online self-education tool for patients with epilepsy, Parkinson's disease and multiple sclerosis called "Confidence College".

The next article is from Julie Jones from Aberdeen, Katherine Baker from Newcastle and Bhanu Ramaswamy from Sheffield who review the evidence for physical therapy in Parkinson's disease and provide concrete examples of the types of activities that can be beneficial for patients throughout the disease course.

Mark Baker and Timothy Wilkins from Newcastle and Andrew Larner from Liverpool write an entertaining vignette about the life and work of Moritz Heinrich Romberg – a man whose name is familiar to every Neurologist for his eponymous sign, albeit a sign that is commonly misspelt.

ACNR's Epilepsy Editor, Marco Mula, introduces the first of a series of articles looking at co-morbidities in epilepsy with a paper by Guy Leschziner from London on the bidirectional relationship between epilepsy and sleep.

The latest in our sleep series sees Poppy Goldsmith from Manchester and Kirstie Anderson from Newcastle highlighting the lack of evidence that psychostimulants such as modafinil are truly "smart drugs" because, although they may boost wakefulness, they may not necessarily enhance memory.

Vestibular migraine is the latest topic to be covered in our headache series. Nitesh Patel, Kulvinder Talewah, Anish Bahra and Diego Kaski from London tease out the clinical features that help to distinguish the condition from important differential diagnoses and provide a guide to treatment.

Our history article from JMS Pearce elucidates the anatomy and significance of the auricular branch of the vagus nerve or "Arnold's nerve".

The conference reports are from Louise Blakeborough reviewing the UKABIF 2021 conference and "The Social Determinants of Neurological disease: Tackling Inequalities" meeting is reviewed by Christina Mousele, Alastair Noyce, Ruth Dobson and Charles Marshall. Giulia Attard Navarro and Charles Fry review the "20th Annual King's Neuromuscular Symposium".

Our book reviews are from AJ Larner reviewing Mario Mendes' 'The Mental Status Examination" and medical student Paliah Malekahmadi who reviews "Nolte's The Human Brain" by Todd Vanderah and Douglas Gould.

We hope you enjoy this edition of ACNR.

Todd Hardy, Co-Editor
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Cover image credit: Sean Keating, Queensland Brain Institute, The University of Queensland, 2021.

PhD student Sean was awarded second place in the 2021 QBI Art In Neuroscience Image Competition with this image "If you truly love nature neuroscience, you will find beauty everywhere", a neuron and astrocyte infused recreation of Vincent van Gogh's 'The Starry Night'.

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Confidence College – an online education tool for neurology patients

By Heather Angus-Leppan, Alice Caulfield, Melika M Moghim, Jennifer Nightingale, Rob Sloan, Tom Stables, Michael Oates, Bernadette Porter and Anette Schrag

Abstract

COVID-19 and its aftermath highlight the importance of patient self-care and involvement in monitoring and improving their health. Resources to guide this are essential.

Our objective was to create a web-based patient education tool, to facilitate patient education and empowerment for people with epilepsy, multiple sclerosis and Parkinson's disease, available without cost to patients, carers and clinicians.

This project was conducted within community and secondary neurology services. Patients and their carers were involved in designing, reviewing and revising the tool, as equal partners with clinicians and digital engineers.

A web-based design template was developed with graphics and links to enable patients to create personalised plans. Participants are patients, carers, clinicians (neurology consultants and specialist nurses), neurological charities, the London Neuroscience Clinical Network, NHS England and Shift.ms (a service design team with experience in creating digital services for individuals living with neurological conditions). Shift.ms conducted in-depth interviews. Clinicians used evidence from personal and PubMed databases. Shift.ms analysed and co-ordinated the responses, and designed the pilot tool.

Confidence College provides a delivery model for patient education relating to multiple sclerosis, epilepsy and Parkinson's disease. It requires follow-up evaluation regarding uptake.

This web-based accessible patient empowerment tool has no limit on recurrent use, low maintenance costs and no additional costs in up-scaling the number of users. It is ideally suited for use during and after the COVID-19 pandemic.

Neurological disorders are amongst the most common chronic medical conditions, affecting an estimated 1 billion people worldwide. Of the 10 million in the UK, approximately 300,000 have active epilepsy, 137,000 have Parkinson's disease, and 85,000 have multiple sclerosis (MS) [1]. Their burden outweighs their point prevalence, as reflected in measures such as disability-adjusted life years (DALY); for example, MS is the leading cause of non-traumatic neurological disability in young adults [2]. There is a significant treatment gap, widened since the pandemic [1]. A World Health Organization (WHO) survey of 155 countries found that almost half of the patients with chronic diseases missed their regular medical care and medications since COVID-19 pandemic began [3].

Patient empowerment enables people to gain control over decisions and actions affecting their health. It emphasises self-efficacy, self-awareness, confidence, coping skills and health literacy [4]. It aims to maximise quality of life and treatment effectiveness and is an important aim for both ethical and economic reasons: treatment non-adherence costs the Healthcare system in the United Kingdom alone an estimated $500 million per year [4], and these figures are echoed throughout the world.

Patient empowerment is primarily achieved through education and communication. Coaching and facilitated support groups improve outcomes and are part of development aims of government healthcare schemes. Increasing patient empowerment in a cost-effective and sustainable way is challenging, as it is difficult and costly to test and upscale potential methodologies. In neurology, barriers to face-to-face educational programmes include disabilities, mobility problems, employment, transport and mood, and currently the restrictions associated with the pandemic [3]. Telemedicine is now used in more than 60% of the world, and use of online resources during the COVID-19 pandemic potentially helps vulnerable individuals to receive care and education without compromising safety.

This project developed online modules to increase accuracy and depth of patient knowledge, designed to enable them to tailor individual health plans with clear goals. Developing evidence-based and user-friendly online patient-focused modules is time-consuming, and depends on collaboration between users and providers. This article outlines the process involved in producing these for three long-term neurological illnesses: multiple sclerosis, epilepsy and Parkinson's disease.

Multiple sclerosis

Surveys of MS services by University College London partners (an academic health science network) highlight regional variations in standards of care and treatment gaps [5]. Individuals with MS, carers and families expressed a desire to improve their confidence in self-management but lacked the necessary tools. Confidence College evolved from this need, in collaboration with the London Neurology Network. Face-to-face courses are expensive in time and resources and are not accessible to all, especially during the COVID-19 pandemic. Online education offers universal access, and flexibility around employment, transport, and family commitments in this generally young population. The project was extended in a second phase to epilepsy and Parkinson's disease.

Epilepsy

Roughly 19-44% of patients with epilepsy are non-adherent to treatment. This increases mortality risk threefold, and increases health costs. Past attempts to improve adherence targeted Applications and e-pill boxes, but forgetfulness is the problem in only 24% of patients. Other factors include perceived unaffordability, underestimating the need for medication, and side effects. An in-depth survey in patients with epilepsy highlighted knowledge gaps, with only 50% aware of sudden unexpected death in epilepsy, and 38% aware of status epilepticus. A greater awareness of the importance of medication adherence (98%) and seizure triggers (84%) suggests a major cognitive dissonance. Solutions to address this education imbalance require an interactive process. The Modular Service Package Epilepsy (MOSES) is an innovative comprehensive group educational module for epilepsy. A randomised trial in Germany showed it reduced seizures in participants [6]. In the UK, qualitative benefit was demonstrated but there were difficulties with attendance, memory and concentration [7]. Online interactive educational resources aim to reduce these barriers.

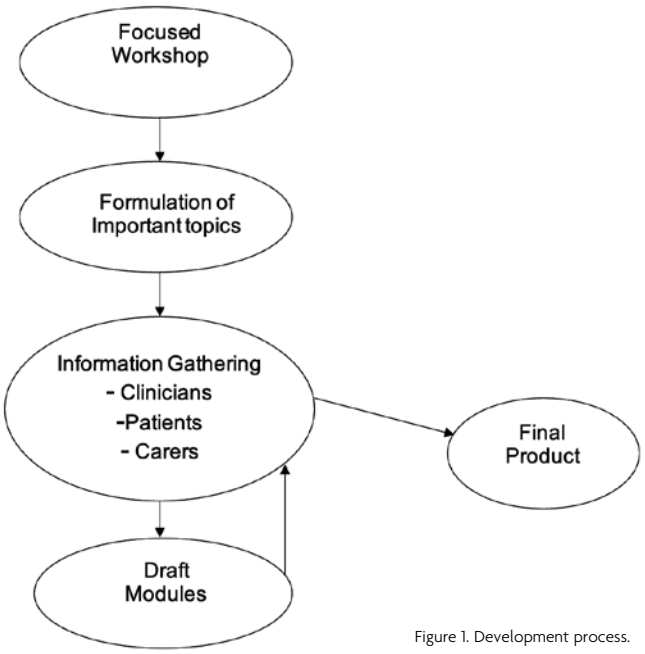

Figure 1. Development process.

Parkinson's disease

Parkinson's disease is highly variable, so information is required on the many features and management strategies. While a holistic, multidisciplinary approach is desirable, a minority of patients have access to such care. Qualitative research suggests that many healthcare professionals consider self-management in Parkinson's disease as important but identify barriers such as lack of resources [8], and research in this field is currently limited [9]. Face-to-face self-management courses are available through charities and peer-support. However, these have limited reach, depending on local availability, are not suitable for all, and are time limited.

Methods

Confidence College is a collaboration between NHS England, Shift.ms (a technological company developing patient-centred educational tools) and NeuroResponse® (a digital health community interest company) for the original MS work.

The development process was iterative, led by clinicians in each specialty, and involved reviewing the clinical information, individual interviews with patients regarding their chief concerns and information needs, and multi-disciplinary focus groups (Figure 1). Three topics for each condition were chosen for this pilot and developed into modules.

Results

Confidence College is accessible through http://www.confidencecollege.org.

Multiple sclerosis

Is it a relapse?

Approximately 85% of individuals with MS present with relapses. Symptoms vary in presentation, severity and impact. They include weakness, visual disturbance, fatigue, cognitive problems, and any other symptom associated with MS. Relapses may have a major impact on family and colleagues. 67% of employed individuals require sickness leave, and 66% need additional support for routine daily tasks [10]. Relapses may occur with no precipitating factor and the speed and extent of recovery is often unpredictable, causing uncertainty.

It can be difficult for both individuals with MS and clinicians to identify a relapse. In this module, individuals and their families learn the definition of a relapse, how to self-monitor and how to differentiate between transient changes in background symptoms and an acute event. This section empowers patients to recognise features of a relapse and feel confident to report them to clinicians.

Figure 2. Visualisation of online modules for MS patients.

Know your bladder

Urinary tract infections are recorded in 13%-80% of patients with MS. They are amongst the top three reasons for hospitalisations in MS, accounting for 30%-50% of all in-patient admissions [11].

Recognising UTI symptoms in a person with MS can be difficult since typical symptoms may be absent and the presentation may be non-specific malaise. Symptoms suggestive of UTI in the general population (urinary frequency and incontinence) may reflect chronic lower urinary tract dysfunction and not signify infection.

The aim of this module is to promote adequate fluid intake, increase early detection of UTIs, use of a urine dipstick, and improve confidence in reporting symptoms to clinicians.

Better plans, better care

This section is shared across all three conditions and aims to empower patients by equipping them with confidence to express their needs to clinicians. It emphasises the need for individuals to identify personal goals that are unique and reflect their values. This potentially allows patients and carers to use their community and hospital consultations to maximum advantage.

Epilepsy

Living Well

This module gives illustrative information about what an epileptic seizure is, what happens to an individual with epilepsy, and what they can do to improve their epilepsy and care, in terms of lifestyle and medication.

It enables patients to develop their understanding of why and how seizures develop. This potentially reduces patients' anxiety, particularly about the unpredictability of seizures. Better understanding seizures can have a positive impact on managing epilepsy, such as enhancing treatment adherence and reducing emergency department visits.

Mind Matters

The second module discusses links between epileptic seizures, mood and behavioural changes, and offers ways to cope with unpleasant thoughts.

Better plans, better care

Here, the care planning documents are discussed, allowing people to individualise them, ask the most useful questions at their neurological reviews, and establish epilepsy goals.

Parkinson's disease

Living Well

This module has three sub-sections. The first, "What happens to the brain?" provides an illustrated overview of Parkinson's disease, explains the motor and non-motor symptoms, and the unique disease impact experienced by individuals. The second, "Parkinson's profile", provides a template for individuals to create a structured record of their own illness, starting with how Parkinson's affects them, and factors that worsen and alleviate their symptoms. The third, "What can I do?", highlights evidence-based variables that patients can influence: medication, lifestyle and exercise. The aim is that patients become expert in understanding their condition, including differentiating between Parkinson's symptoms and treatment side-effects.

Mind Matters

Mood is affected in at least 30% of patients [12]. This section, based on cognitive behavioural principles, focuses on understanding mood and unpleasant thoughts. Links to free online resources are provided to help patients and their carers formulate improvements.

Better plans, better care

This contains templates for a personal description of the patient's life, and their goals, with the aim of personalising treatments and consultations.

Discussion

Confidence College is a collaboration between patients, carers and neurology clinicians, government and charities. It has developed online tools to support self-management in three neurological conditions: multiple sclerosis, epilepsy and Parkinson's disease.

As part of the next stage of development, links to Confidence College will be offered to charity and NHS organisations, with the aim of embedding it into patient resources.

Conclusion

These tools facilitate patient empowerment by enabling individuals to gain a greater understanding of their condition, and through creating personalised health plans.

The use of Confidence College allows patients to prepare for consultations, or carry out in their own time and will not add to the length of consultations. Gathering data on usage is part of the next stage of the research.

Practice implications

This approach has the major advantage of having potential for wide scale use without additional costs: the structure and contents are enduring as it is hosted by NHS England but is available to all. It focuses on self-management of the most significant issues among people with chronic neurological conditions, rather than on new treatment development. These modules are however pilot tools and require long-term testing with a wide representative population to establish utility and impact on care and can be developed further. Future developments may involve adding other topics identified as valuable by the user community. If proven to add value, Confidence College could provide a template for such tools in other disease areas.

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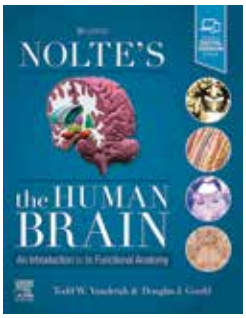
We confirm all patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified through the details of the story.

Nolte's The Human Brain



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This book is aimed at students and teachers alike.

The anatomy of the brain and nervous system more generally are covered in great detail. Useful pathophysiology is presented in vignettes, for example, Brown Séquard syndrome and myasthenia gravis. Clinical focus boxes which provide an overview of neuropathology and neuropharmacology are new features of the 8th edition. For my preference, they might have been more numerous.

Some of the more appealing chapters of the book include those on blood supply to the brain, synaptic transmission between neurons, the spinal cord and eye movements. A clear writing style is used throughout the book and concepts are explained concisely. A glossary has been provided which defines the key terms succinctly. References are included at the end of each chapter. A multitude of images and diagrams are used by the author which help the reader gain a better understanding of the function of the human brain and the anatomy. The book contains two atlases, one of the human forebrain and another of the brainstem only, with annotated diagrams demonstrating the different areas of the forebrain and brainstem. Perhaps similar resources, for the cerebellum and cord, could have been added.

A unique feature is that the reader can gain access to a range of multiple-choice questions that have been designed for each chapter, however, these are available online only. And although the book is a great source for any university student wishing to study the brain in detail, it falls down as a tool for revision through the lack of summary sections.

Overall, this a very good book which is easy to recommend.

HOW DURABLE IS THE RESPONSE TO FINTEPLA (FENFLURAMINE) IN DRAVET SYNDROME?

Dravet syndrome is a rare and lifelong form of epilepsy that has a significant burden on patients and their families[1,2]

A recent survey of 584 people with Dravet syndrome found that a high seizure frequency is associated with more comorbidities and a low quality of life[2]

Patients generally take multiple AEDs, however <10% are seizure-free[2,3]

Early seizure onset is associated with poor cognitive and neurodevelopmental outcomes, for which tonic seizures, early myoclonus appearance and absences are the main negative prognostic factors[4,5]

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.[6]

In Phase 3 trials, Fintepla provided a profound reduction in seizure frequency for people with Dravet syndrome.*[7,8] The durability of this result was recently demonstrated in a long-term extension study[9] and a real-world compassionate use programme[10]

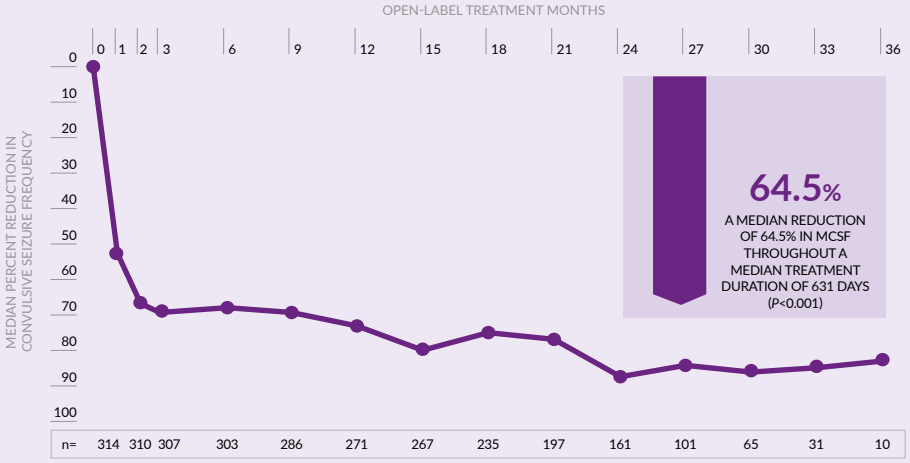
3-YEAR INTERIM ANALYSIS OF AN ONGOING, LONG-TERM, OPEN-LABEL EXTENSION STUDY[9]

As of 14 October 2019

Patients aged 2–18 who had successfully completed one of three Phase 3 studies[7,8,11] were eligible

- Fintepla reduced the median monthly convulsive seizure frequency (MCSF) by 64.5% from baseline to up to 3 years (P<0.001)
- Fintepla was generally well-tolerated with no observations of valvular heart disease or pulmonary arterial hypertension
  - 3.3% of patients discontinued treatment due to an AE
  - The most common AEs were pyrexia (28.2%), nasopharyngitis (27.3%), decreased appetite (23.0%), blood glucose decreased (19.4%), diarrhoea (18.2%), seizure (16.7%) and upper respiratory tract infection (15.5%)

The profound reduction in seizure frequency demonstrated in the Phase 3 trials*[7,8] was maintained for up to 3 years[9]



n=330 at the interim analysis cut off date (14 October 2019)
631 days median Fintepla treatment duration (range 7–1086)

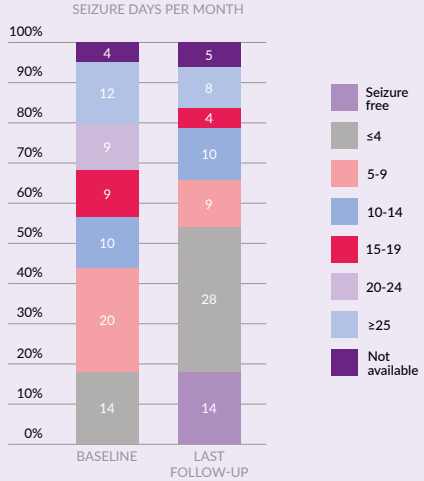
Mean daily dose of Fintepla ranged between 0.3 and 0.7mg/kg/day for 70% of patients.
The decrease in patient number is primarily due to staggered entry into the study and not due to patient withdrawal.

GERMAN COMPASSIONATE USE PROGRAMME[10]

78 children and adults ≥2 years of age receiving Fintepla for Dravet syndrome were monitored for a median of 255.5 days (range 31–572)

- In the 3 months before Fintepla initiation, the median number of seizure days per month was 10.0, which decreased to 3.0 in the last 3-month period of treatment (*P*<0.001)
- Other results indicated clinically meaningful reductions in seizure rates at 3, 6 and 12 months of treatment, an improvement in the Clinical Global Impression of Change for 89% of patients and an overall reduction in use of concomitant AEDs
- Fintepla was generally well-tolerated with no observations of valvular heart disease or pulmonary arterial hypertension
  - 5% of patients discontinued treatment due to an AE
  - The most common AEs were somnolence (36%), decreased appetite (22%) and ataxia (8%)

Overall, the study provides valuable information on the use of Fintepla in clinical practice.



Fintepla provides durable, long-term reduction in seizure frequency for people with Dravet syndrome[9,10]

To find out more or to speak to a member of our team, email us at: **UKteam@Zogenix.com**
For further information please visit **www.Fintepla.eu**.

*Study 1: a randomised, double-blind, placebo-controlled clinical trial to assess the safety and efficacy of adjunctive Fintepla in Dravet syndrome. 119 patients were randomised 1:1:1 to placebo (n=40), Fintepla 0.2mg/kg/day (n=39) or Fintepla 0.7mg/kg/day (n=40) for 14 weeks. Patients treated with Fintepla 0.7mg/kg/day experienced a 62.3% greater reduction in MCSF than placebo ($P<0.0001$; primary endpoint).[7]

Study 2: a randomised, double-blind, placebo-controlled clinical trial of Fintepla as part of a stiripentol-inclusive AED regimen in Dravet syndrome. 87 patients were randomised 1:1 to placebo (n=44) or Fintepla 0.4mg/kg/day (n=43) for 15 weeks. Patients treated with Fintepla experienced a 54.0% greater reduction in MCSF than placebo ($P<0.001$; primary endpoint).[8]

AE, adverse event; AED, anti-epileptic drug.

Fintepla▼ (fenfluramine) Prescribing information

Please refer to the full Summary of Product Characteristics (SmPC) before prescribing. **Indications:** Treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. **Presentation:** 2.2 mg/mL oral solution. Each mL contains 2.2mg of fenfluramine (as fenfluramine hydrochloride). **Dosage and Administration:** Please refer to SmPC for full information. *Patients who are **not** taking stiripentol:* Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). After 7 days, if tolerated, can increase dose to 0.2 mg/kg twice daily (0.4 mg/kg/day). After an additional 7 days, if tolerated and further seizure reduction required, can increase dose to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day), which is the recommended maintenance dose. Patients requiring more rapid titration may increase the dose every 4 days. Do not exceed maximum daily dose of 26 mg (13 mg twice daily). *Patients who are taking stiripentol*: Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). After 7 days, if tolerated, can increase dose to 0.2 mg/kg twice daily (0.4 mg/kg/day), which is the recommended maintenance dose. Patients requiring more rapid titration may increase the dose every 4 days. Do not exceed a total dose of 17 mg (8.6 mg twice daily). *Discontinuation*: When discontinuing treatment, decrease the dose gradually. As with all anti-epileptic medicines, avoid abrupt discontinuation when possible to minimize the risk of increased seizure frequency and status epilepticus. *Special populations: Renal impairment:* No clinical data available. *Hepatic impairment:* No clinical data available. Not recommended in moderate or severe liver impairment. *Elderly*: No data available. *Paediatric population:* Safety and efficacy in children below 2 years of age not yet established. No data available. **Contraindications:** Hypersensitivity to active substance or any excipients. Aortic or mitral valvular heart disease and pulmonary arterial hypertension. Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome. **Warnings and Precautions:** *Aortic or mitral valvular heart disease and pulmonary arterial hypertension:* Prior to starting treatment, patients must undergo an echocardiogram to establish a baseline and exclude any pre-existing valvular heart disease or pulmonary hypertension. Conduct echocardiogram monitoring every 6 months for the first 2 years and annually thereafter. If an echocardiogram indicates pathological valvular changes, consider follow-up earlier to evaluate whether the abnormality is persistent. If pathological abnormalities seen on echocardiogram, evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver and cardiologist. If echocardiogram findings suggestive of pulmonary arterial hypertension, perform a repeat echocardiogram as soon as possible and within 3 months to confirm these findings. If echocardiogram finding is confirmed suggestive of an increased probability of pulmonary arterial hypertension defined as intermediate probability, conduct a benefit-risk evaluation of continuation of Fintepla by the prescriber, carer and cardiologist. If echocardiogram suggests a high probability, it is recommended fenfluramine treatment should be stopped. *Decreased appetite and weight loss:* Fenfluramine can cause decreased appetite and weight loss - an additive effect can occur in combination with other anti-epileptic medicines such as stiripentol. Monitor the patient's weight. Undertake risk-benefit evaluation before starting treatment if history of anorexia nervosa or bulimia nervosa. *Fintepla controlled access programme*. A controlled access programme has been created to 1) prevent off-label use in weight management in obese patients and 2) confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking Fintepla. *Somnolence*: Fenfluramine can cause somnolence which could be potentiated by other central nervous system depressants. *Suicidal behaviour and ideation.* Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic medicines in several indications. Advise patients and caregivers to seek medical advice should any signs of suicidal behaviour and ideation emerge. *Serotonin syndrome:* Serotonin syndrome, a potentially life-threatening condition, may occur with fenfluramine treatment, particularly with concomitant use of other serotonergic agents; with agents that impair metabolism of serotonin such as MAOIs; or with antipsychotics that may affect the serotonergic neurotransmitter systems. Carefully observe the patient, particularly during treatment initiation and dose increases. *Increased seizure frequency*: A clinically relevant increase in seizure frequency may occur during treatment, which may require adjustment in the dose of fenfluramine and/or concomitant anti-epileptic medicines, or discontinuation of fenfluramine, should the benefit-risk be negative. *Cyproheptadine*: Cyproheptadine is a potent serotonin receptor antagonist and may therefore decrease the efficacy of fenfluramine. If cyproheptadine is added to treatment with fenfluramine, monitor patient for worsening of seizures. If fenfluramine treatment is initiated in a patient taking cyproheptadine, fenfluramine's efficacy may be reduced. *Glaucoma.* Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Discontinue therapy in patients with acute decreases in visual acuity. Consider discontinuation if ocular pain of unknown origin. *Strong CYP1A2 or CYP2B6 inducers*. Co-administration with strong CYP1A2 inducers or CYP2B6 inducers may decrease fenfluramine plasma concentrations. Consider an increase in fenfluramine dosage when co-administered with a strong CYP1A2 or CYP2B6 inducer; do not exceed the maximum daily dose. *Excipients*.Contains sodium ethyl para-hydroxybenzoate (E 215) and sodium methyl para-hydroxybenzoate (E 219) - may cause allergic reactions (possibly delayed). It also contains sulfur dioxide (E 220) which may rarely cause severe hypersensitivity reactions and bronchospasm. Patients with rare glucose-galactose malabsorption should not take this medicine. The product contains less than 1 mmol sodium (23 mg) per the maximum daily dose of 12 mL; essentially 'sodium-free'. Contains glucose - may be harmful to teeth. **Drug interaction**: Pharmacodynamic interactions with other CNS depressants increase the risk of aggravated central nervous system depression. Examples of such depressants are other serotonergic agents (including SSRIs, SNRIs, tricyclic antidepressants, or triptans); agents that impair metabolism of serotonin such as MAOIs; or antipsychotics that may affect the serotonergic neurotransmitter systems. Co-administration with CYP2D6 substrates or MATE1 substrates may increase their plasma concentrations. Co-administration with CYP2B6 or CYP3A4 substrates may decrease their plasma concentrations **Pregnancy and lactation**: *Pregnancy:* Limited data in pregnant women. As a precaution, avoid use of Fintepla in pregnancy. *Breast-feeding:* It is unknown whether fenfluramine/metabolites are excreted in human milk. Animal data have shown excretion of fenfluramine/metabolites in milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fintepla taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Ability to drive and use machines:** Fintepla has moderate influence on the ability to drive/ use machines as it may cause somnolence and fatigue. Advise patients not to drive or operate machinery until they have sufficient experience to gauge whether it adversely affects their abilities. **Undesirable effects:** *Very common (≥1/10):* Bronchitis, upper respiratory tract infection, decreased appetite, lethargy, somnolence, status epilepticus, tremor, constipation, diarrhoea, vomiting, pyrexia, fatigue, blood glucose decreased, echocardiogram abnormal (trace regurgitation), weight decreased and fall. *Common (≥1/100 to <1/10):* Ear infection, abnormal behaviour and irritability. Refer to SmPC for other adverse reactions. **Overdose:** Limited data concerning clinical effects and management of overdose. Agitation, drowsiness, confusion, flushing, tremor (or shivering), fever, sweating, abdominal pain, hyperventilation, and dilated non-reactive pupils were reported at much higher doses of fenfluramine than those included in the clinical trial program. Treatment should include gastric lavage. Monitor vital functions closely, and administer supportive treatment in case of convulsions, arrhythmias, or respiratory difficulties. **Package quantities and Marketing Authorisation number**: Fintepla is presented in a white bottle with oral syringes included which should be used to administer the prescribed dose. Bottle sizes of 60 mL, 120 mL and 360 mL. EU/1/20/1491/001, EU/1/20/1491/002 and EU/1/20/1491/004. **Legal Category:** POM. **Marketing Authorisation Holder:** Zogenix ROI Ltd, Trinity House, Charleston Road, Ranelagh, Dublin 6 D06 C8X4 Ireland. **Maximum NHS List Price:** Bottle sizes of 60mL = £901.44, 120mL = £1802.88 and 360mL = £5408.65

Job Code: UK- FIN1-2100051 **Date of Preparation:** August 2021

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Physical activity and exercise for people with Parkinson's

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Abstract

A growing body of evidence exists advocating the value of physical activity and exercise for people with Parkinson's. Such is the importance of being active, participation in exercise is perceived to be of equal importance to medication in the long-term management of Parkinson's. Despite a substantial body of evidence, the optimal prescription of exercise or mode of delivery remains underdetermined. This article aims to discuss the current evidence and provide guidance of prescription of exercise during each of three commonly-referred to stages of Parkinson's: newly diagnosed, maintenance and complex.

Introduction

Parkinson's is the fastest growing neurological condition, with a 50% predicted rise of people living with the condition by 2030 [1]. In the absence of a cure, interventions that aim to limit the rate of decline and promote quality of life are of paramount importance to researchers and clinicians alike. Interest in the value of physical activity (PA), including exercise, has grown exponentially due to its potential neurorestorative role, as well as its positive impact on slowing the rate of decline. It is therefore essential that all members of the multi-disciplinary team are aware of the benefits of both for people with Parkinson's and can promote participation in activity by signposting individuals to local PA opportunities. This paper summaries the PA evidence and describes PA prescription of each of three commonly-referred to stages of Parkinson's: newly diagnosed, maintenance and complex.

Physical activity is an umbrella term which encompasses bodily movements produced by skeletal muscles, including a wide range of behaviours like gardening, housework and leisure-related activities [2]. Exercise is a subcategory of physical activity, defined as activities which are planned, structured, and purposeful, with the intention of improving and/or maintaining one or more components of physical fitness [3]; the terms Exercise and Physical activity however are commonly used interchangeably and inconsistently in activity-based research.

Diagnostic stage

PA should form an integral part of Parkinson's management from diagnosis, and should be perceived as of equal importance to medication, not as complementary [4]. Owing to the heterogeneous nature of Parkinson's, a personalised approach to PA is advocated [5]. Key messages at this stage are to promote a physically active focused lifestyle, supported by friends and the Parkinson's community, to support the development of a long-term activity habit. Exercise should be prescribed in tandem with contextualised education, to support changes in physical activity behaviour, and to provide people with Parkinson's with the knowledge and skills to self-manage their physical activity.

When prescribing physical activity, frequency, intensity, type of activity and time need to be carefully considered. Within the diagnostic phase exercise prescription should focus on supporting people with Parkinson's to develop a regular physical activity habit of a minimum of 2.5 hours a week [6], developing confidence to participate in higher intensity exercise is also advocated at the early stages of Parkinson's. Participation in moderate to high intensity exercise (65-85% of mHR) has been shown to be both safe and feasible for people with Parkinson's [7] and is associated with potential neurorestorative effects. Animal studies and a small number of human-based studies have demonstrated that high intensity exercise promotes improved vascularisation through angiogenesis, as well as increased concentration of neurotrophic factors such as BDNF or GDNF which are essential for neuronal growth, and integrity [5]. 150 minutes of moderate to high intensity exercise is advocated such as Nordic walking, aerobics, and cycling each week.

Types of exercise should be varied reflecting the range of motor and non-motor symptoms that people present with, combined with individual preferences. Reflecting current guidelines, strength training should be undertaken two to three times a week targeting spinal, hip and knee extensors and ankle dorsiflexors, prescribed in a progressive manner, where both resistance and task complexity are incrementally increased [8]. Flexibility training should be undertaken twice a week focusing on the spine, upper and lower limbs, ensuring that amplitude of movement is maintained during functional tasks [4]. Similarly balance training should be conducted twice weekly including turning, and dynamic movements incorporating progressive dual and cognitive tasks [8]. Figure 1, the exercise wheel acts as a guide on the frequency and types of exercise to guide physical activity engagement.

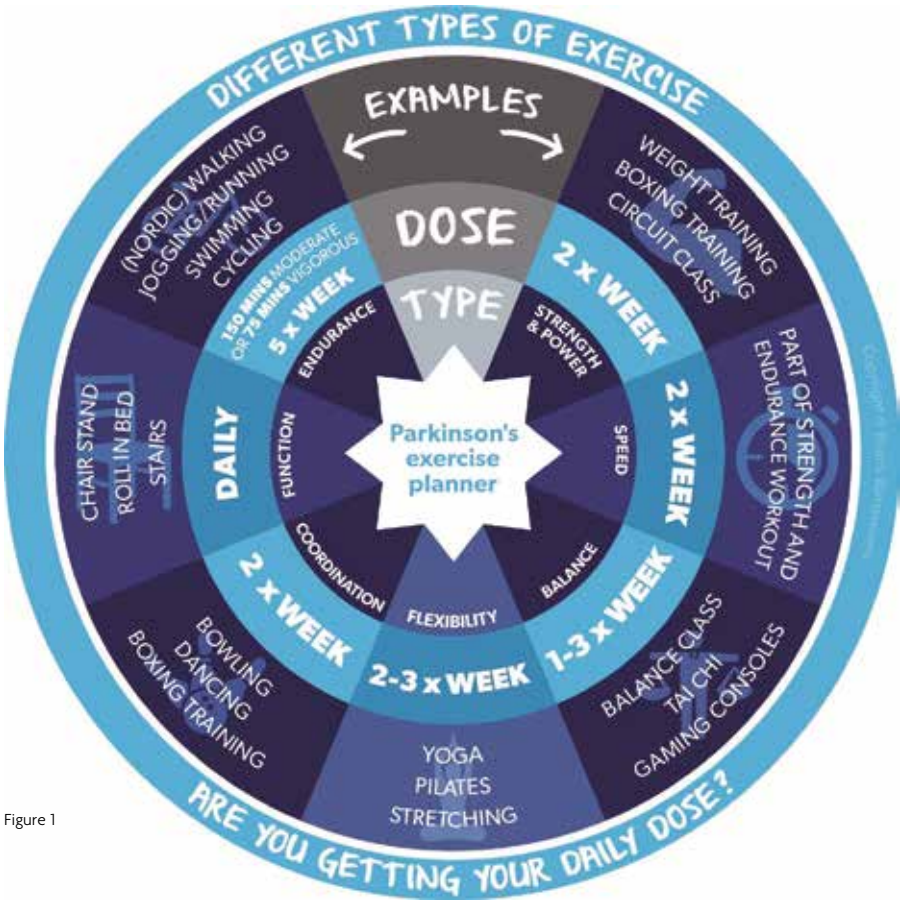

Figure 1

Maintenance stage

Following on from the diagnosis stage, it remains important to continue with general PA and advice in the maintenance stage to keep the person fit and active for as long as possible. Progression of the condition can reduce physical capacity and mobility, which can lead to inactivity; these issues can be improved with exercise [8] but it is also important to recognise that they make exercising more challenging. Increasing severity of motor symptoms such as bradykinesia, compromising joint range of movement and strength, and the combined effects of rigidity and tremor alter the biomechanics of movement and impair balance. Collectively these symptoms reduce PA levels which can lead to muscle atrophy, joint stiffness, and reduced physical capacity.

It is also important to remember the influence of other conditions and non-motor symptoms including apathy, fatigue, pain and fear of falling which may become more problematic in this phase. Recognising these increasing barriers to exercise [4] emphasises the importance of addressing motivation and using a person-centred approach [5,9,10]. Creating a routine is very important when establishing consistent PA behaviour, but as symptoms may become a little more unpredictable it may be important to have options so the individual always has a manageable exercise plan relevant to how they feel.

While the principles of PA introduced in the diagnosis phase remain important, the approach used to achieve this may need to be adapted. Parkinson's specific programmes which address motor and non-motor symptoms more explicitly may be helpful [11]. Individuals should be supported to maintain or increase their level of activity and to engage with activities which target flexibility and focus on posture and balance. The individual should be supported to maintain the effort with which they are active while also ensuring that body and mind are engaged so as to preserve memory, attention and learning and to aid the management of non-motor symptoms such as sleep and mood. Exercise professionals should be aware that motor symptoms can put individuals at risk of injury so care should be taken to prepare individuals appropriately for PA. Activity should be conducted when medication is optimised and it is important to regularly review and adapt the PA programme.

Later stage

The longer a person has Parkinson's, interventions should combine exercise, movement strategies and cues so they can function even when in the 'off' state [12]. In the later stages of Parkinson's, co-morbidities increase and people reduce physical activity and exercise performance levels, which have been associated with higher rates of all-cause mortality [13].

Little quantitative research exists to demonstrate the benefits of continuing exercise past Hoehn and Yahr Phase 3 due to the increasing complexity of the condition, however, the lived experience of people with Parkinson's repeatedly illustrates the importance of maintaining an exercise routine for both physical and mental health, particularly if unable to access their usual programmes [14].

The people with Parkinson's and those supporting them, who contributed towards the development of the Parkinson's UK Exercise Framework spoke of the difficulties in maintaining a sufficient dosage of exercise to manage physical challenges as their condition progressed, but some exercise was viewed as essential in preserving fitness and functional daily activities where possible and managing the discomfort from likely postural changes [15]. Alterations to physical and mental ability necessitate an emphasis on increased support from others to assist the person with Parkinson's with exercise, particularly for transfers and gait related activities [16]. As mobility impairments compromise safety, exercise should become more chair based using free weights and stationery equipment e.g. pedallers, plus be supervised to a greater extent [17].

Whilst still adhering to the Parkinson's-specific principles of exercising at maximal effort, amplitude and power, attention should be paid to the following:

1. Ensuring that functional movement is a key component of exercise routines e.g. sit to stand, turning in bed, overcoming episodes of freezing – all of which may need additional training of movement strategies or cuing techniques.
2. Respiratory complications are the highest cause of mortality in people with Parkinson's. As bradykinesia and rigidity affect lung function [18], respiratory exercises should be added to any exercise routine [19].

Conclusion

Physical activity should form an integral part of the management of people with Parkinson's from diagnosis. Like medication, physical activity prescription needs to reflect individual needs, and should encompass strength, flexibility, balance, aerobic, and functional based exercise. Physical activity should be prescribed in parallel with contextualised education to provide the person with adequate knowledge and skills to develop a sustained physical activity habit.

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Heather Angus-Leppan receives International Research award for Royal Free Charity neurology study

Heather Angus-Leppan, Consultant Neurologist and Epilepsy Lead at the Trust, and Theme 2 director, has won the 2021 "Eminent Scientist and outstanding scholar" Award by the International Research Promotion Council (IRPC). The award is for her research on Valproate. The study, published in *Acta Neurologica*, "Valproate risk form—Surveying 215 clinicians involving 4775 encounters" (https://doi.org/10.1111/ane.13231) assessed the uptake, successes and pitfalls of the govern-mandated change in policy and the compulsory risk acknowledgement form that all women who want to continue taking Valproate must complete. Balancing the rights of women and their unborn children is complex, and it is known that Valproate can cause serious malformations in the unborn child if women take it during pregnancy. On the other hand, for some women it is the only medication that controls their epilepsy. Women need to be informed of the risks of alternate medication, as this study showed that those changing from Valproate to alternatives had a 30-40% risk of breakthrough seizures which can be serious and, very occasionally, fatal.

Dr Angus-Leppan worked with Dr Melika Moghim, then a Royal Free medical student, and a national team including Professor Rohit Shankar, Professor Hannah Cock, Dr Lucy Kinton and Marie Synnott-Wells on this study. A follow up study is planned for late 2022.

Heather is extremely grateful for the support of the Royal Free Charity who funded this study, and the NIHR who support part of her salary. She would be delighted to answer questions and share copies of the research publication for those interested, and can be contacted through her email address – rf.epilepsyteam@nhs.net.

ILAE British Branch – Gowers Awards Essay Competition

Deadline – Friday 1st July 2022.

Entries are invited for the Gowers Awards Essay Competition. Dissertations are welcome on any aspect of epilepsy, with awards made in two categories:

Clinical Science Award

This category is open to health professionals working in all clinical specialities related to Epilepsy. Essays might focus on one of a range of topics such as epidemiology, clinical effectiveness, risk, quality of life, sociology, neuropsychology, or other relevant topics. Essays can be up to a maximum of 5,000 words and can be on any topic of clinical epilepsy (but cannot have been published or submitted for publication elsewhere). There is an award of £500 for the best submission and the ILAE British Branch will fund your registration, attendance at the Annual Scientific conference dinner in Cardiff and accommodation costs to attend the conference (Travel not included).

Medical Student Award

Submissions are welcome from FY1s as long as the work was completed as a medical student. There is an award of £500 for the best submission and the ILAE British Branch will fund registration, attendance at the conference dinner and accommodation costs to attend the Annual Scientific Meeting. You will be invited to present your work at the meeting and there may be an opportunity for winning essays to be published in *Seizure*.

More information can be found at https://bit.ly/3KbE8vz

Rehabilitating Romberg

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Few Neurologists will be unfamiliar with referral letters stating that the patient has "Rhomberg's sign" or some "mild rhombergism" (capitalisation variable), a particularly irritating misnomer for the pedants among us. As Henry Higgins the fictional Professor of Phonetics [1] observed:

'Does the same thing hold true in India, Pickering? Is there the peculiar habit of not only dropping a letter like the letter "h", but using it where it doesn't belong, like "hever" instead of "ever"?' My Fair Lady – Act 1, Scene 5, p58 [1].

Or Rhomberg instead of Romberg!

So, who was "Rhomberg," and what did he describe?

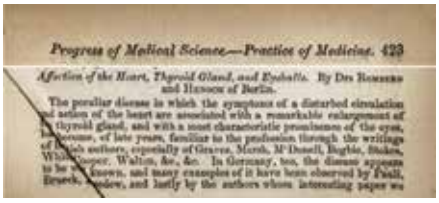
The Neurologist: a brief biography [2,3,4]

Of course, all neurologists know (or should know) that the eponymous clinician is in fact Romberg, specifically Moritz Heinrich Romberg (Figure 1A). Born in Saxony in 1795, he studied in Berlin and Vienna before pursuing his career in Berlin (at the Charité Universitätsmedizin) from 1820 until his retirement in 1867. He has been described as one of the founders of neurology, principally on account of his book, Lehrbuch der Nervenkrankheiten des Menschen, published between 1840 and 1846. This has been characterised as the first formal treatise on diseases of the nervous system, which aimed to link pathology and physiology systematically. Therein, Romberg gave one of the enduring accounts of tabes dorsalis and described the pupillary findings in tertiary syphilis (before the eponymous Argyll Robertson).

Elsewhere he gave a classic description of achondroplasia, and published on diverse medical and surgical topics, co-authoring papers with his nephew Eduard Heinrich Henoch (Figure 1B, C) [5].

Figure 1A. Moritz Heinrich Romberg (1795-1873) [From https://en.wikipedia.org/wiki/Moritz_Heinrich_Romberg].

Figure 1B. Eduard Heinrich Henoch (1820-1910) not only described the IgA-mediated vasculitic non-thrombocytopenic rash that became known as Henoch-Schonlein Purpura but was also Romberg's nephew. [From https://en.wikipedia.org/wiki/Eduard_Heinrich_Henoch].



Progress of Medical Science.—Practice of Medicine. 423

Affection of the Heart, Thyroid Gland, and Exophthalmos. By Drs Romberg and Henoch of Berlin.

The peculiar disease in which the symptoms of a disturbed circulation and action of the heart are associated with a remarkable enlargement of the thyroid gland, and with a most characteristic prominence of the eyes, has become, of late years, familiar to the profession through the writings of British authors, especially of Graves, Marsh, M'Dowell, Begbie, Stokes, White Cooper, Walshe, &c. &c. In Germany, too, the disease appears to be well known, and many examples of it have been observed by Friedl, Breslau, Basedow, and lastly by the authors whose interesting paper we

Figure 1C. Review of a case series reported by Romberg and his nephew on Graves' disease in the *Edinburgh Medical and Surgical Journal* of 1854 [5].

Eponymous signs [4,6,7]

Romberg is surely best known for his sign, or signs: static, sharpened, psychogenic, and dynamic variants of Romberg's sign have been described, although only the first of these originates with Romberg himself.

His particular contribution was to develop a clinically elicited neurological sign based on the observation that eye closure in patients with tabes dorsalis resulted in a tendency to sway and fall. Others had also observed this phenomenon before Romberg, such as Marshall Hall and Bernardus Brach, but not developed it for use as a sign.

Hence, Romberg's sign, or Rombergism, is adjudged present (or positive) when there is a dramatic increase in unsteadiness, sometimes with falls, after eye closure when a patient is standing comfortably. This is sometimes known as the static Romberg's test, in contrast to dynamic Romberg's test (vide infra). Before asking the patient to close his or her eyes, it is necessary to position one's arms in such a way as to be able to catch the patient should

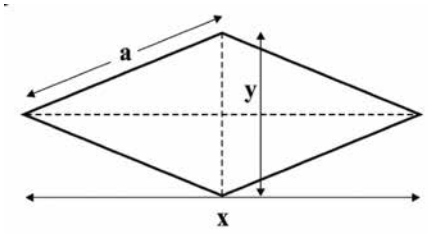


Figure 2. A rhombus, which has the following properties: opposite angles are equal (implying also that the parallelogram law ($4a^2=x^2+y^2$) is satisfied); diagonals (x and y) are perpendicular (i.e. an orthodiagonal quadrilateral); and diagonals bisect opposite angles.

they begin to fall. Patients may fall forward immediately on eye closure ("sink sign").

These phenomena result from sensory ataxia i.e. loss of proprioception from the feet, which occurs most commonly with posterior column spinal cord disease, not limited to patients with tabes dorsalis, in whom Romberg originally described his sign, but which may also occur in other forms of deafferentation.

There is no standardised method of "how to do it" (i.e. operationalisation of the sign), for example whether the feet should be positioned together or apart; whether the feet should be positioned heel to toe, so-called "sharpened Romberg's sign" (narrowing the standing base); whether or not shoes should be worn; the duration of observation; and how much sway indicates a positive sign. Posturography is an attempt to quantify the Romberg test.

A modest increase in sway on closing the eyes may be seen in normal subjects, and in patients with cerebellar ataxia, frontal lobe ataxia, and vestibular disorders (toward the side of the involved ear); on occasion these too may produce an increase in sway sufficient to cause falls. Hence, Romberg's test is not specific.

Large amplitude sway without falling, due to the patient clutching hold of furniture or the Neurologist, has been labelled "psychogenic Romberg's sign", an indicator of functional stance impairment.

It has been argued that Romberg's sign is neither highly sensitive nor specific (no dedicated test accuracy study has been reported to our knowledge) and, because of the risk of falling, should be abandoned in favour of testing proprioception at the big toe [8].

Heel-toe or tandem walking, walking along a straight line by putting one foot directly in front of the other, heel to toe, as on a tightrope, is sometimes known as the "dynamic Romberg's test". Impairment in this test may be a consequence of ataxia of either cerebellar or sensory origin.

Pryse-Phillips also lists "Romberg's spasm" as a form of masticatory spasm of unknown cause, probably dystonic [9].

Eponymous syndromes

Romberg's name is recorded (second) in at least two syndromes, both somewhat esoteric.

Parry-Romberg syndrome is progressive hemifacial atrophy due to loss of subcutaneous tissues [10,11]. In addition to the cosmetic features, ipsilateral intracerebral abnormalities may also occur, producing neurological features such as migraine, facial pain, focal seizures, hemiparesis, hemianopia, and cognitive impairment. The condition was first described by the English physician Caleb Hillier Parry (1755-1822) in the posthumously published Collections from the unpublished medical writings of the late Caleb Hillier Parry MD FRS (1825; volume I, p.478-80). Romberg's account appeared over 20 years later, in 1846.

The Howship-Romberg syndrome [12], or phenomenon (widely and incorrectly referred to as a sign [13,14]) is pain or paraesthesia in the hip or groin radiating along the anteromedial thigh to the knee provoked by extension, abduction and medial rotation of the lower limb (and thus an inability to adduct the thigh) due to irritation/compression of the obturator nerve by an obturator hernia. The association of small bowel obstruction and the Howship-Romberg phenomenon is recognised amongst general surgeons to be pathognomonic of an incarcerated obturator hernia [14]. The condition was originally described by the English surgeon John Howship (1781-1841), whilst working at St George's Hospital (Lanesborough House, Hyde Park Corner, London), around 1840.

We suspect that few Neurologists will have encountered either of these syndromes during their careers.

So why the confusion?

Why confuse "Romberg" with "Rhomberg"? The frequency of misspelling has been previously noted [8], and indeed it has been claimed that this is the most misspelled eponym in neurology [4]. We suggest some possible explanations.

Firstly, very simplistically: homophony. In neurology, terminology incorporating the word 'rhombus' (Figure 2) is more frequent. For example, the rhomboid muscles, major and minor, and the rhombencephalon (Figure 3) [15]. Moreover, the letter rho (þ) is also used as both the mathematical symbol for density and to denote Spearman's correlation coefficient.

Secondly, and probably related to the first point: familiarity. Whilst we do not suggest that rhombus is a high frequency word, Romberg is certainly lower frequency. Whereas Romberg is unlikely to be encountered prior to medical school or even, possibly, neurological training, the rhombus is a staple of

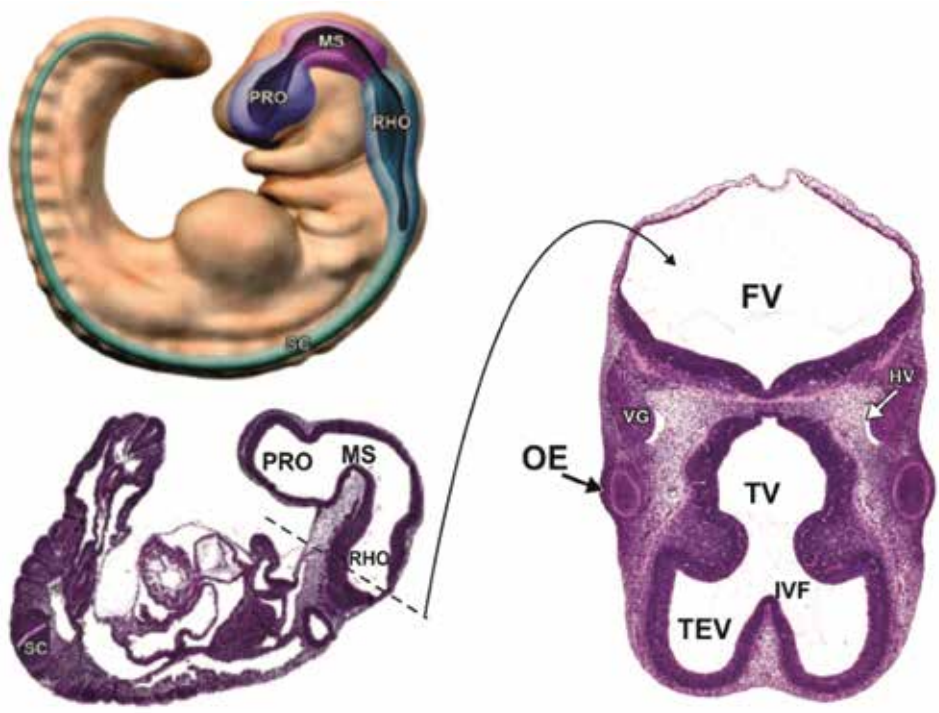


Figure 3. The rhombencephalon (RHO), which gives rise to the pons, medulla and cerebellum, is known embryologically thus because when sectioned transversely (dashed line) the developing neural tissue surrounding the fourth ventricle (FV) forms a rhombus.

HV = head vein; IVF = interventricular foramen; MS = mesencephalon; OE optic eminence; PRO = prosencephalon; SC = spinal cord; TEV = telencephalic vesicle; TV = third ventricle; VG = trigeminal ganglion (adapted from Figures 3 and 11 of Chen et al., 2017) [15].

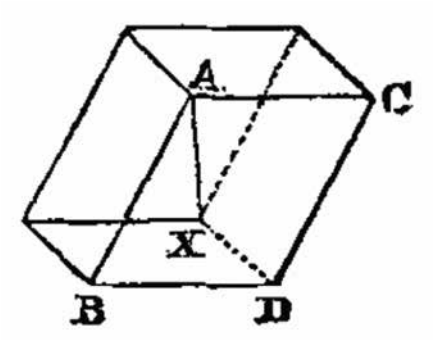


Figure 4A. Necker's Rhomboid reproduced from page 336 of his original description of the optical phenomenon [17].

Figure 4B. An image of Louis Albert Necker de Saussure (1786-1861), maternal great great nephew of Charles Bonnet (1720-1793), aged 20 (modified from Eyles, 1948) [18].

Figure 4C. Necker's grave at Portree, Isle of Skye, photographed by Robin Campbell (from Wade et al., 2010 [19]).

even primary school geometry. Hence the latter is more familiar and this might account for the substitution. The hint of the esoteric or mathematical might link to the general unfamiliarity (or unwillingness to become familiar) with matters neurological.

Thirdly, and related to the previous point: as a medical community we have become increasingly ignorant of our history, collectively consigning many of the great Neurologists of the past, including Professor Moritz Heinrich Romberg, to obscurity. Although, as shown by the preceding brief biography, a case can be made for including him in the neurological pantheon, he is not well known, or well-served by eponymous association, even though his textbook was translated into English in 1853 by Edward Sieveking, a physician at Queen Square. Sadly, his German origin might also account for his obscurity in the Anglophone world, wherein ignorance of other languages approaches the normative (and may also account for such lapses as "L'hermitte" for "Lhermitte", and hence to references to "the hermit's sign" [16]).

For those sorry to lose "Rhomberg" from the neurological lexicon, we offer some possible consolation. Necker's cube, the optical illusion, drawing or copying of which features in certain cognitive screening instruments (e.g. the various iterations of the Addenbrooke's Cognitive Examination), was in fact a rhombohedron, or what is more commonly termed a rhomboid, rather than a cube (Figure 4A) [17] in the original publication of 1832 by Louis Albert Necker (1786-1861; Figure 4B & 4C) [18,19]. As cube is to rhomboid as square is to rhombus, perhaps we should (more correctly) rename this "Necker's rhomboid".

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The Comorbidities of Epilepsy: Introduction

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Epilepsy is one of the most frequent neurological disorders after stroke and headache, affecting over 70 million people worldwide, and it is now widely accepted that having epilepsy does not simply mean having recurrent seizures. In fact, epilepsy rarely stands alone and more than 50% of patients with epilepsy have one or several additional medical problems [1]. This is reflected in the new multiaxial classification of the epilepsies of the International League Against Epilepsy that includes comorbidities along with seizure types, aetiologies and syndromic classification [2].

The word "comorbidity" dates back to Alvan Feinstein who introduced this term in 1970 referring to any distinct additional clinical entity that existed during the clinical course of a patient's index disease [3]. However, in the context of epilepsy, the term "comorbidity" includes a heterogenous group of conditions whose pathophysiology can be quite different [4]. Some conditions may coexist simply because one is the cause of the epilepsy like, for example, stroke and epilepsy or neurocisticercosis and epilepsy. In other cases, the condition is the consequence of having epilepsy or its treatment like for example osteoporosis and epilepsy or sexual dysfunction and epilepsy. Still, some conditions may share with epilepsy a common aetiology, like autism and epilepsy in the context of Tuberous Sclerosis Complex, or may be linked by a more complex bidirectional relationship like epilepsy and depression.

Whether these problems are due to shared biological mechanisms, a consequence of having epilepsy or simply due to the unfortunate occurrence of two conditions in the same individual, there is no doubt that the management of these patients can be challenging [4]. This can be due to the potential for drug-drug interactions that Neurologists need to be aware of or because the comorbid disorder has an impact on the epilepsy and its management. In fact, comorbidities do not simply affect quality of life of patients but also represent prognostic markers and affects health costs resulting in increased hospitalisation rates, longer hospital length of stay, frequent health-care visits and, ultimately, higher health-related costs [5].

In order to develop successful therapeutic interventions and prevention strategies, it is important to have a clear understanding of the pathophysiology of comorbidities and the magnitude of the problem. The identification, treatment and prevention of comorbidities should become an integral part of epilepsy care and epilepsy centres should lead on the development of treatment guidelines, prevention policies and structured referral pathways for the management of these conditions that can be easily implemented by Neurologists in everyday clinical practice.

This series of articles will explore some among the most frequent and sometimes challenging comorbidities in epilepsy. Focus will be on current research and clinical management. These articles are authored by distinguished experts in the field. I do hope that these articles will stimulate further interest in this area, leading to constant improvements in the care of our patients.

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Table 1. Types of comorbidities of epilepsy

Type	Mechanism	Examples	Management
Causative	One is the cause of the other	Stroke; Traumatic brain injury; CNS infections (eg. neurocysticercosis, HIV); Multiple sclerosis; Brain Tumours; Heart diseases	Tailored treatment strategies; prevention of drug-drug interactions
Reciprocal	One is associated with increased risk of developing the other and vice versa (complex multifactorial reasons)	Mood and anxiety disorders; Psychosis; ADHD; Autism Spectrum Disorder; Irritable bowel syndrome; Headaches; Psychogenic non-epileptic seizures; Diabetes; Suicide	Screening for early diagnosis and management
Mutual	Shared risk factors or aetiological mechanisms	Tuberous sclerosis; Cerebral palsy; Autoimmune encephalitis; Intellectual disabilities; Anti-GAD antibody associated type 1 diabetes; Dementia; Headaches; Heart diseases	Precision medicine and disease modifying agents
Resultant	Caused by seizures and their treatments	Sexual dysfunction; Obesity; Osteoporosis; Heart diseases; Obstructive sleep apnoea syndrome; Type 2 diabetes	Screening and prevention strategies
Coincidental	By chance	Any condition	Tailored treatment strategies; prevention of drug-drug interactions

HIV=Human immunodeficiency virus; ADHD=attention deficit hyperactivity disorder; CNS=Central nervous system; GAD=glutamic acid decarboxylase

Seizures and sleep: Not such strange bedfellows

Abstract
It has long been recognised that sleep and deprivation of it have important consequences for cortical excitability, the electroencephalogram and seizure control. However, in the management of people with epilepsy, it is also important to recognise that epilepsy and its treatment may also have significant implications for sleep. Lack of consideration for this bidirectional relationship between sleep and epilepsy may have negative consequences on individuals' seizure control, quality of life, and other aspects of their health.

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The fact that sleep and epilepsy are intimately related is evident in clinical practice. Many patients in the epilepsy clinic exhibit close links between sleep and their seizures. Indeed, this association extends to our investigation of epilepsy, with the recognition that sleep deprivation and sleep itself may accentuate epileptic features on the electroencephalogram (EEG), and that EEG recordings in these states may increase sensitivity and yield.

There is growing evidence that management of sleep disorders and the improvement of sleep quality may influence seizure frequency and other outcome measures. Despite this, for persons with epilepsy and sleep complaints, there is a tendency to ascribe symptoms such as fatigue, tiredness or excessive daytime sleepiness, to anti-seizure medications, rather than questioning whether they may be due to a sleep disorder. Conversely, epilepsy and its management may also influence sleep. Insomnia as an adverse effect of anti-epileptic drugs (AEDs) is also frequently under-recognised, and epileptic discharges may disrupt sleep or even trigger parasomnias.

It is clear therefore that the relationship between sleep and epilepsy is bidirectional. In view of the prevalence of sleep disorders, consideration of sleep should be included in the routine management of patients with epilepsy.

The effects of sleep on epilepsy

Sleep, its various stages, and the circadian rhythm may all influence aspects of epilepsy. A number of epilepsy syndromes in childhood and adulthood exhibit a predilection for seizures arising from or shortly after sleep. In the paediatric setting, these include benign epilepsy with centro-temporal spikes (also known as benign Rolandic epilepsy), with up to 59% of patients having exclusively sleep-related seizures, Panayiotopoulos syndrome, Electrical Status Epilepticus in Slow Wave Sleep, Landau-Kleffner syndrome and infantile spasms [1]. In adults, the archetypal sleep-related epilepsy syndrome is that of frontal lobe epilepsy, in the autosomal dominant genetic form associated with mutations in nicotinic acetylcholine receptor subunit genes, while the myoclonic jerks of juvenile myoclonic epilepsy tend to occur in the morning, shortly after waking. In some individuals with genetic generalised epilepsy (GGE), generalised seizures will exclusively occur shortly after waking.

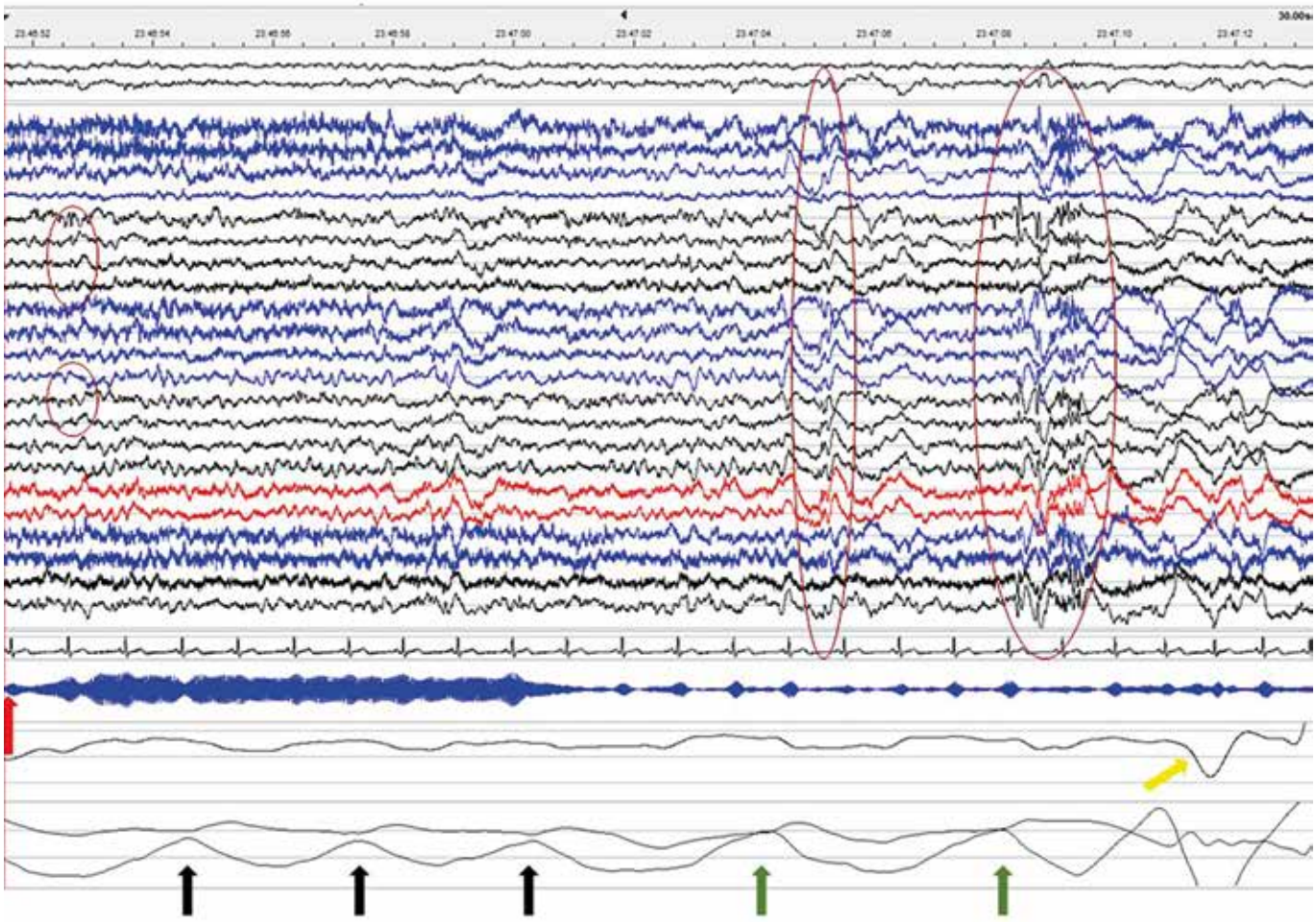
Beyond specific epilepsy syndromes, seizures often follow a circadian pattern, presumably related to the effects of circadian rhythms on brain activity. Seizures arising from different brain locations appear to have different patterns. For example, mesial temporal and occipital lobe seizures in adults are more likely to occur in the mid-afternoon, while seizures of parietal or frontal lobe origin are more likely to occur in the early hours of the day [2]. These data have been gathered both from the analysis of in-hospital telemetry and long-term out-patient recordings from implanted neurostimulators [3].

Two mechanisms have been proposed to mediate the influence of the circadian rhythm on seizures [4]. Firstly, clock genes such as BMAL1 and CLOCK contribute to epileptic excitability. Secondly, the mammalian target of rapamycin (mTOR) pathway is regulated by the circadian timing system. The mTOR pathway has been implicated in a range of neurological disorders, including epilepsy.

The stages of sleep also have a profound impact on epilepsy. Seizures, and indeed epileptic abnormalities on the EEG, are rarely seen in rapid eye movement (REM) sleep [5]. Even in non-REM sleep, seizures are more likely to arise from non-REM stage 1 (N1) and stage 2 (N2) sleep, and occasionally patients do exhibit a marked tendency to have seizures when non-REM sleep is unstable, particularly when transitioning from deeper to lighter stages of non-REM sleep.

Disruption of sleep as a result of behaviour or through sleep disorders is a frequent precipitant of seizures. Of the provoking factors described by almost all patients with epilepsy, acute and probably chronic sleep loss is the most frequently cited, and of course in the clinical setting, acute sleep deprivation is utilised in an attempt to provoke seizures or to accentuate interictal epileptiform discharges on the EEG. Obstructive sleep apnoea (OSA) is also increasingly recognised as an important factor in epilepsy control. Several studies have reported a high prevalence of OSA in epilepsy patients [6], with some indication that prevalence is higher than in the general population [7]. Approximately one third of patients with drug-resistant epilepsy have obstructive sleep apnoea (OSA), and OSA is correlated with poorer epilepsy control. A recent pilot study comparing continuous positive airway pressure (CPAP) against sham demonstrated a larger reduction of seizure frequency in the CPAP group, and in a further study, CPAP adherence resulted in a reduction of seizure frequency that was not seen in those patients that were non-adherent. Similar findings have been reported in children with epilepsy and

Figure 1. Thirty second epoch from a combined PSG-EEG in a patient with an implanted vagus nerve stimulator for drug--refractory epilepsy. The VNS fires for 9 sec (red arrow), precipitating three obstructive events (black arrow, showing paradoxical chest and abdominal movements), followed by two partial obstructed breaths, (green arrow), before an arousal and restoration of a patient airway (yellow arrow). Epileptic discharges are circled. (With thanks to Sean Higgins and Michalis Koutroumanidis).



OSA; adenotonsillectomy was associated with a reduction in seizure frequency. Proposed mechanisms for this association include sleep fragmentation and chronic sleep loss, EEG arousals and intermittent hypoxaemia. Insomnia has also been associated with more frequent seizures, depressive symptoms and poorer quality of life [8].

Effects of epilepsy on sleep

Epilepsy may directly or indirectly – through its management - influence sleep. In individuals with epilepsy, both excessive daytime sleepiness and sleep fragmentation are common complaints, and up to half report insomnia. Sleep disorders are common in the general population, and thus it is not surprising that they are common in patients with epilepsy either. However, there are some sleep issues specifically related to individuals with epilepsy. Nocturnal seizures may result in significant sleep fragmentation, and may precipitate arousals generating non-REM parasomnias such as confusional arousals or even sleep-walking. Furthermore, nocturnal epileptic activity may be mistaken for non-REM parasomnias.

Daytime seizures may also influence sleep architecture and levels of sleepiness, both subjectively as reported by patients and through objective measures such as maintenance of wakefulness testing [9].

The treatment of epilepsy is also a common cause of sleep disturbance. It is well-recognised that the majority of AEDs may cause sleepiness, but the weight gain associated with some AEDs may increase the risk of sleep-disordered breathing, and drugs like lamotrigine and levetiractam can precipitate severe insomnia in a small proportion of individuals. AEDs can also have varying effects on sleep architecture, differentially altering proportions of light and deep non-REM sleep and REM sleep [10]. Vagus nerve stimulation may also disrupt sleep, with stimulation triggering central or obstructive apnoeic events or stridor [11].

Evaluation of sleep in the individual with epilepsy

In the management of persons with epilepsy and sleep complaints, particularly sleepiness, it is important to recognise that co-morbid sleep disorders are more likely to be the driver than the epilepsy or the AEDs prescribed [12]. Therefore, while it is obviously relevant to focus on the epilepsy and medication regimen, a clinical assessment in the form of a sleep history should be undertaken. While many validated sleep questionnaires exist, there are none specific to epilepsy. These can be used for screening purposes, e.g. the Sleep Condition Indicator (an eight-item rating scale for insomnia), or the Pittsburgh Sleep Quality Index (useful for prompting an exploration of several different domains of sleep). These questionnaires however should not be seen to replace a full history. The Epworth Sleepiness Scale is a useful clinical tool for measuring subjective sleepiness, with a score of 10 or more viewed as pathological, and a very low score perhaps suggesting insomnia. Short questionnaires such as STOP-BANG can aid screening for OSA.

In addition to correlating the temporal relationship between sleep symptoms, seizure control and medication changes, the history should focus on the rapid identification of co-morbid sleep disorders, for the purposes of a consultation in the epilepsy clinic. Areas of particular relevance include the ascertainment of adequate sleep opportunity, difficulties in initiating or maintaining sleep, features of obstructive sleep apnoea such as loud snoring, witnessed apnoeas, nocturia, or a dry mouth, sore throat or headache on waking, or symptoms of restless legs syndrome such as nocturnal urge to move and periodic limb movements of sleep or wake.

Table 1: Common effects of AEDs on sleep symptoms /disorders		
AED	**Improves**	**Worsens**
Lamotrigine (LTG)	–	Insomnia
Levetiracetam (LEV)	–	Fatigue / Somnolence OSA [a]
Carbamazepine (CBZ)	Insomnia	Fatigue / Somnolence
Sodium Valproate (VPA)	Insomnia	Fatigue / Somnolence
Phenytoin (PHT)	–	Fatigue / Somnolence Insomnia
Topiramate (TPM)	OSA [b]	–
Pregabalin (PGB)	Insomnia	Fatigue / Somnolence OSA [a]
Gabapentin (GBP)	Insomnia	Fatigue / Somnolence OSA [a]
Phenobarbitone (PHB)	Insomnia	Fatigue / Somnolence OSA [a]
Lacosamide (LAC)	–	Fatigue / Somnolence
Zonisamide (ZON)	OSA [b]	Fatigue / Somnolence
Perampanel (PER)	Sleep architecture	Fatigue / Somnolence OSA [a]
Oxcarbazepine (OXC)	–	Fatigue / Somnolence
Ethosuxamide (ETH)	OSA [b]	–
Benzodiazepines (BZP)	Insomnia	Fatigue / Somnolence OSA
Brivaracetam	–	Fatigue / Somnolence
Cenobamate	–	Fatigue / Somnolence
Cannabidiol*	Sleep architecture	Fatigue / Somnolence / Sleep disturbance
(a) – due to weight gain; (b) – due to weight loss; *There are limited and conflicting data		

Table adapted from Dennis GJ. "The relationship between sleep and epilepsy." Adv Clin Neurosci Rehabil 2016;16(2):13-16.

The investigation of sleep disorders in patients with epilepsy does not necessarily require expensive specialist technology, although for some patients combined polysomnography and EEG is necessary; it should be noted that standard polysomnography only provides four channels of EEG, which is rather limited for the full evaluation of patients with epilepsy. A simple sleep diary may help identify those patients who are behaviourally sleep-restricted or have insomnia, while home respiratory testing ranging from simple overnight oximetry to full-respiratory polygraphy will be sufficient to diagnose most cases of sleep-disordered breathing and periodic limb movement disorder. In-patient or home video-telemetry is generally utilised in those individuals with unusual behaviours at night, where epileptic arousals or seizures are suspected, or in those in whom a co-morbid hypersomnia of central origin is in the differential.

Management

In patients with epilepsy with a sleep complaint, the first step is to ensure that a possible iatrogenic cause is reversed if possible. Phenobarbital is considered the most sedating, but most AEDs can precipitate or worsen sleepiness, and a temporal relationship between symptoms and prescribing should be sought. Insomnia is particularly associated with lamotrigine and levetiracetam, but may also be seen with other drugs that are more typically associated with sedation, such as pregabalin [13].

In the absence of clear drug causality, co-morbid sleep disorders should be treated [14]. Insomnia may be improved through cognitive behavioural therapy for insomnia [15] (CBTi), the gold-standard first line treatment for insomnia disorder [16]. In epilepsy however, standard CBTi should be modified to replace sleep restriction, which may provoke seizures, with sleep compression. Group CBTi, widely practised in the NHS, may not be appropriate for this cohort of patients as a result. Pharmacological approaches include utilising AEDs that may shorten sleep latency, e.g. pregabalin, gabapentin, perampanel, or standard treatments for insomnia such as melatonin, or sedating antidepressants. Prolonged release melatonin in particular is viewed as a relatively safe long-term pharmacological therapy for insomnia, although its efficacy in epilepsy has thus far only been demonstrated in children [17]. Benzodiazepines and Z-drugs such as zopiclone should only be prescribed for up to two weeks where the primary indication is insomnia, although occasionally clobazam can be helpful.

OSA should be managed in the same vein as in the general population, with one or two exceptions. Weight loss is effective in the management of OSA [18], and this can sometimes be facilitated by the weaning of AEDs predisposing to weight gain, or rarely initiation of topiramate (topiramate in conjunction with phentermine has been demonstrated to show both reduction in body-mass index and apnoea-hypopnoea index in a placebo-controlled trial [19]). Mandibular advancement devices are widely used for mild OSA, but the author's own practice is to studiously avoid usage in an individual with epilepsy, for fear of obstructing the airway during a nocturnal seizure, unless there is no alternative. Epilepsy is usually seen as a contraindication, but there are some case reports of well-fitting devices being used, and the author is aware that not all clinicians take this view, particularly with bespoke devices that fit well and are less likely to be displaced. Continuous positive airway pressure is the treatment of choice, and as described above, may have significant benefits on seizure control.

Other conditions like restless legs syndrome (RLS) and periodic limb movement disorder are best managed utilising alpha-2-delta ligand (gabapentinoid) AEDs that are also widely adopted, if unlicensed, treatments. These drugs are increasingly being proposed as first-line treatments for RLS in international guidelines [20]. There are obviously concerns regarding illicit use, and these drugs should be given once nightly, and at the lowest dose possible. However, these drugs should be used cautiously in patients with primary epilepsy syndromes as they may worsen or indeed precipitate the new onset of absences and myoclonic seizures. In these cases, treatment with dopa agonists or clonazepam (also unlicensed) may be preferable.

Conclusion

Sleep problems are extremely common in patients with epilepsy, and beyond simply influencing quality of life, can have a significant impact on seizure control, cognition and mood. Therefore, the recognition and management of sleep disorders should be an essential aspect of the review of patients in the epilepsy clinic.

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Psychostimulants as cognitive enhancers – the evidence for the use and abuse of smart drugs

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Abstract
While modafinil is licensed to treat narcolepsy as a psychostimulant, there is widespread use as a "smart drug" in the young to help study and interest in older populations as a cognitive enhancer. This review considers both the evidence for benefit and potential for harm. If it is as effective as it seems, should we all be using it? Should Neurologists recommend it, and should we worry if our patients are taking it? In this review the evidence base behind psychostimulants, in particular modafinil as a cognitive enhancer, is discussed.

Psychostimulants such as modafinil and methylphenidate are prescribed to treat CNS hypersomnias including narcolepsy and in the US, residual sleepiness due to obstructive sleep apnoea and shift work sleep disorder [1]. However, they are also widely used as smart drugs in those without sleep disorders to help concentration and memory, in particular modafinil. Modafinil is the most widely prescribed psychostimulant for narcolepsy and there is off-licence use in depression, older populations, and neurodegenerative disease for both alertness and cognition. Healthy individuals using modafinil as a stimulant report increased concentration and attention; facilitating harder and longer hours of study and work. Contrary to other traditional psychostimulants, like amphetamines, modafinil has few reported side effects, low potential for tolerance or dependence and is relatively safe to use [1]. It is widely available online.

What is modafinil?

Modafinil is a psychostimulant drug that increases wakefulness and has been licensed since 1994. The precise mechanism remains debated, but it acts as an atypical, selective and weak dopamine reuptake inhibitor alongside inhibition of noradrenaline reuptake. It also indirectly activates the release of orexin neuropeptides and histamine and inhibits GABA thereby increasing arousal and alertness. Elevated levels of circulating catecholamines are responsible for behavioural arousal [1].

Modafinil has chemical and physiological effects that differ from amphetamines. Amphetamines have far greater impact on motor activity with a shorter half life than modafinil [1]. This may explain why modafinil has fewer side effects than other traditional stimulants with very low potential for tolerance or dependence. It does have some unwanted side-effects including hypertension (dose initiation but no evidence for sustained increase in blood pressure compared to placebo), headache for up to 20% and increased anxiety with palpitations for some. Furthermore, the long 12-15 hour half-life undoubtedly increases the likelihood of insomnia [2]. Modafinil can decrease efficacy of the combined oral contraceptive pill and increase the risk of congenital malformation when used during pregnancy. These are notable interactions considering the potential overlap in users of modafinil and contraceptives [3]. The prescribed dose ranges from 100mg to 400mg a day in one or two divided doses.

Who is using it?

Almost a million prescriptions are currently issued in the United States per year and approximately 80,000 within the UK despite licensed use only for narcolepsy [4]. These patients are very likely to be the tip of the iceberg. In the UK it is legal to buy but not to sell modafinil. An abundance of websites can be found selling modafinil from around 60 pence a tablet with 5-star reviews accompanied with a word of warning about avoiding delivery direct to student halls of residence! A 2017 Global Drug Survey reported that 6.6% of participants used prescription pharmacological cognitive enhancing drugs (PCE) for non-medical purposes [5]. The most typical users of modafinil are employed, male, university graduates [6]. The unregulated nature of use means that it is not clear whether people are using it for an 'all-nighter' before an assignment is due or more frequently in the day to constantly enhance performance.

What is the evidence base for cognitive enhancement?

There have now been many randomised controlled trials studying cognitive measures in those using modafinil versus placebo, both in healthy non-sleep deprived individuals and those who were sleep deprived. Typically, this is a single dose of either 100mg-400mg. A wide variety of cognitive batteries have been used with variable results.

A meta-analysis and systematic review in 2019 looked at 19 trials and found a significant but small effect (hedges' g 0.10) across numerous cognitive domains. There was no difference across different cognitive domains and no difference between 100mg and 200mg [7]. Modafinil has been compared to the world's best loved stimulant caffeine and also to methylphenidate and dexamphetamine. Both modafinil and caffeine increase extracellular catecholamine concentrations to

promote wakefulness. Caffeine is an adenosine blocker, indirectly increasing catecholamine levels but with more widespread physiological effects alongside more variable peak plasma and elimination levels. A recent meta-analysis comparing modafinil, methylphenidate and dexamphetamine versus placebo in healthy, non-sleep deprived individuals looked at 47 studies [8]. There was no benefit from dexamphetamine, only a small benefit in sustained attention for methylphenidate and improved attention and some sub domains of memory for modafinil. Variability to both study design and results was highlighted by the authors.

There is more convincing evidence that modafinil improves attention and executive function in sleep deprived subjects [9]. Sleep deprivation causes deficits in alertness and attention but also executive function. Executive functions include the cognitive abilities necessary to plan and coordinate actions, to monitor and adjust behaviour as necessary, and to focus attention and suppress distractions. Total sleep deprivation reduces many of these functions, including the ability to think divergently and to switch flexibly among semantic categories. Results demonstrating benefit of modafinil have been replicated over several simple task studies, particularly those that test sustained attention and reaction speed, for example the psychomotor vigilance test (PVT). The PVT is a simple reaction speed test to visual stimuli that is one measure of alertness. A delayed reaction is seen with sleep deficit.

Some have pointed out that those using modafinil as a study drug are unlikely to be performing simplistic tasks. For example, synthesising information and using it to write an essay may be completed quicker and to a higher standard with modafinil, but this is difficult to reproduce in research.

Executive function and processing speed has a small but significant improvement after taking modafinil. There is less evidence for different domains of memory including problem solving tasks and creativity, which in some studies was worse [10]. If the intended outcome of taking modafinil is an enhanced processing speed to aid completion of an occasional project started too close to a deadline, it may have a use. However, modafinil may offer less benefit when studying for prolonged periods and there is simply far less data that has tested this.

Cognition of course includes executive function but also encoding, sorting, retrieving and then linking up initially fragile short-term memories. Creative thinking is not clearly enhanced by psychostimulants [10]. Long-term side effects accompanying frequent usage may include hypertension but possibly more importantly either cause or allow chronic sleep deprivation. There is increasing interest in poor sleep as an independent risk factor for worse cardiometabolic health and possibly as a dementia risk factor [2]. There is a lack of data regarding the long-term effects of modafinil, particularly in populations without prescription. Most research also concentrates on sleep-disordered subjects, which is not representative of all consumers.

It is also impossible to be certain that drugs ordered online from unregulated sites are authentic. The MHRA estimate that 10% of people in the UK last year purchased 'fake' medical products online [11].

The potential role of modafinil in neurodegenerative disease

Cognitive enhancing drugs such as modafinil may provide therapeutic compensation for the neuronal degeneration seen in an ageing brain. Common symptoms of neurodegenerative disease include excessive daytime somnolence, cognitive decline, and decreased alertness. Modafinil has been used for these symptoms due to its alerting and potentially neuroprotective qualities. Some feel it may have a role in prevention of neurological decline and maintenance of optimal functioning, particularly in the elderly.

The total cost of dementia care in the UK is estimated to be $26 billion with an ongoing search for novel therapies. Catecholamine deficiency is characteristic of many dementias and modafinil triggers an elevation in catecholamine levels - hence its role in controlling symptoms of dementia has been postulated.

Trials in patients with Dementia with Lewy bodies (DLB) showed improvements in subjective attention-span and alertness with modafinil compared to placebo. A preliminary study of 9 patients with DLB or Parkinson's Disease Dementia (PDD) showed mild to moderate improvement in performance in cognitive assessment following modafinil consumption. Investigations included the psychomotor vigilance test, assessment of reaction and reflexive attention tasks [12]. Although there is some evidence for symptomatic improvement, clinicians report limited changes seen in practice at this stage and most trials are preclinical [13]. Some case reports also describe exacerbation of psychotic symptoms due to dopaminergic effects of modafinil [14]. The extent of drug interaction in dementia patients remains unclear.

Modafinil has demonstrated neuroprotective effect in animal models of Parkinson's disease. MPTP induces degeneration of the substantia nigra and is used to model Parkinsonian lesions. MPTP was injected into a primate model and half were also given a dose of modafinil. Animals treated with modafinil had reduced neurotoxin induced neuronal loss and reduced Parkinsonian symptoms, suggesting that modafinil may have roles other than as a psychostimulant [15].

Is there a better smart drug available?

Sleep has been proven to play a key role in memory consolidation and encoding new memories, [16,17]. Anatomical and chemical changes occur during sleep that lead to synaptic downscaling to strengthen new memory formation as the brain is taken off-line. In zebrafish, modafinil increased the number of wake bouts occurring throughout the night, meaning less time spent in a plastic memory-promoting state. Modafinil therefore may aid longer, but not necessarily smarter studying. Following sufficient hours of sleep, the drive to take modafinil may also be reduced. There is a trade-off between the benefits of occasional modafinil use and the detrimental effects of persistent sleep deprivation. Would it be smarter for students to simply utilise the body's free smart drug and power nap before they start writing?

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Vestibular migraine

Abstract

Vestibular migraine is an under-diagnosed but increasingly recognised neurological condition that causes episodic vertigo, associated with migrainous features. Making a diagnosis of VM relies on a clinical history, including the presence of recurrent episodes of vertigo or dizziness, on a background of migraine headaches, and associated migraine features that accompany the vestibular symptoms. It is the most common cause of spontaneous (non-positional) episodic vertigo, affecting up to 1% of the population, but remains under-diagnosed outside specialist centres, partly due to an absence of diagnostic biomarkers. Its pathophysiology remains poorly understood, and there is a paucity of high-quality treatment trials. Here we review the clinical features of vestibular migraine, highlight current theories that account for vestibular symptoms, and outline treatment guidelines.

Vestibular migraine (VM) is a syndrome of episodic recurrent vertigo[1] or dizziness[2] in patients with a current or history of migraine. Previously known as migraine-associated vertigo, migraine-associated dizziness, migraine-related vestibulopathy, migrainous vertigo, the term vestibular migraine perhaps best emphasises the prominent vestibular symptoms upon a background of migraine [1]. In 2012, the International Headache Society and the Barany Society representing the international neuro-otological community published a first consensus on diagnostic criteria for VM (Table 1) [1].

VM remains under-recognised outside specialist centres, before however – only 2% of patients suspected to have VM by non-specialists whereas 20% were later diagnosed as VM by specialists [2]. In the general population, the lifetime prevalence of definite VM has been estimated to be 0.98% [3]. Another population-based study reported a 1-year prevalence of 2.7% [4].

Whether VM and migraine are distinct entities or whether these are two sides of the same coin remains an area of contention. Dizziness and vertigo may be found in up to 30% of people with migraine but a definite diagnosis of VM can be made in 10-21% of migraineurs [5,6]. VM can occur at any age with mean age of onset in middle age and a reported female to male ratio as high as 5:1 [7,8]. Migraine headaches usually precede the onset of vertigo episodes by some years, and typical migraine attacks may be replaced by vestibular episodes (especially in post-menopausal women) [8]. In children, it has been suggested that benign paroxysmal vertigo of childhood is an early manifestation of VM [9].

Pathophysiology

Current models of VM pathophysiology are based on evolving theories of migraine, such as activation and sensitisation of trigeminovascular pathways, as well as brain stem and diencephalic nuclei [10,11]. Based on neurophysiological data, thalamocortical dysrhythmia (TCD) – altered rhythmic activity between thalamus and cortex leading to abnormal information processing – is also considered key to migraine pathophysiology [12,13]. Imaging studies have showed increased activity in the thalamus – known to participate in multimodal sensory sensitisation [14] – during vestibular stimulation in patients with VM [15]. A long-standing hypothesis suggests that VM episodes result from spreading depolarisation [16], akin to 'visual aura', but this cannot account for the more prolonged episodes of dizziness or vertigo commonly seen in VM.

From a molecular perspective, descending pathways from the monoaminergic nuclei control the sensory trigeminal unit, and several neuropeptides, such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP), have essential roles in the activation mechanisms of the trigeminovascular pathways [17]. A differential proinflammatory signature in VM (namely elevated IL-1β, CCL3, CCL22, and CXCL1 levels) appears to differentiate VM from other vestibular disorders such as Ménière's disease [18].

VM, similar to migraine headache, is commonly familial and is widely assumed to have a genetic susceptibility, with combined epigenetic, and environmental contributions [19].

Clinical features

Triggers

In one of the largest studies to investigate triggers in 1027 migraineurs, the commonest trigger was emotional stress (79.7%) [20]. Others have identified sleep disorders (oversleep, lack of sleep, or change in sleep pattern) to be a trigger in 81% [21], but these studies did not include VM as a specific subgroup. A history of anxiety and depression has also been associated with a significantly increased risk of developing VM [4]. Patients with VM often have a significant past history of adverse experiences. This can include a mental health disorder (anxiety in 70%, depression in 40%) [22], as well as adverse experiences associated with migraine and disorders causing nausea and/or dizziness (Figure 1).

Symptoms

The diagnosis of VM relies on the clinical history. Frequently, patients presenting with vertigo do not volunteer a history of migraine, so it is important to specifically enquire about this.

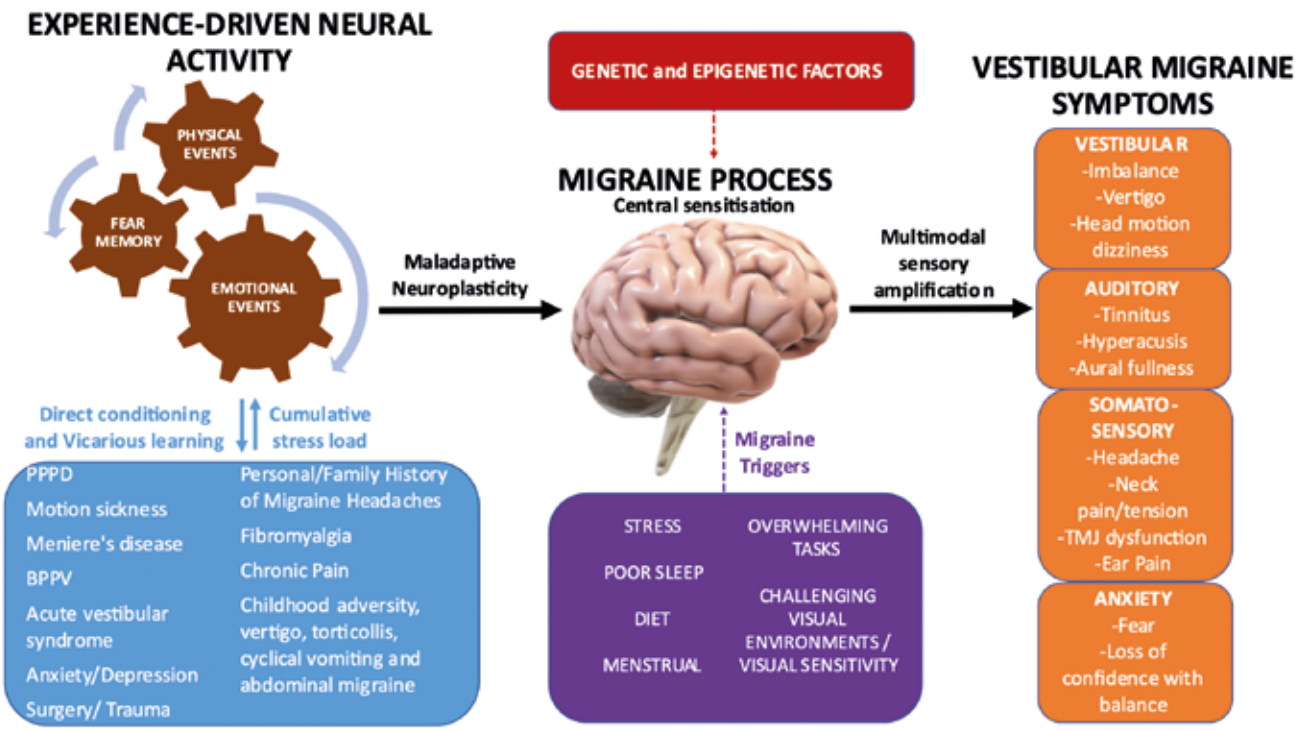

Figure 1: Vestibular migraine is a complex syndrome manifesting vestibular, auditory, somatosensory and anxiety related symptoms. Based on migraine pathophysiology, there is central sensitisation, disordered sensory processing and multimodal sensory amplification which is influenced by genetic, epigenetic, and experience driven neural activity. Various migraine triggers are involved in episodic exacerbations. There may be experience-dependent modulation of neuroendocrine systems to stresses, and the neuroplasticity changes occur in potentially migraine-relevant hypothalamic nuclei, suggesting this could be relevant in migraine and VM pathophysiology [16].

Table 1: Diagnostic Criteria for Vestibular Migraine Proposed by Barany Society and the Third International Classification of Headache Disorders (ICHD-3), 2012

Definite vestibular migraine
A. At least five episodes of vestibular symptoms of moderate or severe intensity lasting 5 min to 72 h
B. Current or prior history of migraine according to the International Classification of Headache Disorders (ICHD)
C. One or more migraine features with at least 50% of the vestibular episodes. This may include migraine headache, photophobia or phonophobia, and visual aura
D. Not better accounted for by another vestibular or ICHD diagnosis
Probable vestibular migraine
a) At least five episodes of vestibular symptoms of moderate or severe intensity lasting 5 min to 72 h
b) Only one of above criteria B and C is fulfilled (i.e., migraine history or migraine features during the episode)
c) Not better accounted for by another diagnosis

The duration of vertigo varies widely from seconds to days, with further episodes occurring after days, months or less commonly, years. Nausea and imbalance are frequent associated features. Vertigo may occur as a prodromal aura before a migraine headache, occur with the migraine headache or independently. Most episodes have no temporal relationship with the headaches. Susceptibility to motion sickness has found to be enhanced in patients with VM [23] and particular attention should be given to a pre-existing history of motion sickness such as being unable to read in the passenger seat of a car due to nausea [24]. Another prominent feature of VM is visually induced dizziness, where challenging visual inputs (i.e., moving images, shopping aisles) can provoke vertigo or spatial disorientation [25]. Positional vertigo can occur with VM and has been reported in 24% of patients, in contrast to 67% of patients describing spontaneous (non-positional) episodic vertigo [26]. Head motion-induced dizziness has been described as a unique feature of VM [22] but is seen in patients with unilateral and bilateral vestibulopathies also. Persistent, almost constant dizziness has been reported in 51.1% of patients with VM [22], but such patients have more likely transitioned into persistent postural-perceptual dizziness (PPPD) – a functional neurological disorder characterised by persistent non-vertiginous dizziness and/or unsteadiness [27].

Audiological symptoms are commonly reported by patients with VM and can include otalgia, tinnitus, aural fullness or pressure and subjective hearing change in more than two-thirds of patients [28]. Hyperacusis [29], and fluctuating hearing loss has also been described [30].

Additional clinical history should include any migraine-specific precipitants of vertigo attacks including menstrual cycle, sleep disturbance, emotional stress, sensory stimuli (e.g. bright lights, intense smells and noise) [31].

Signs

Clinical examination in patients with VM is typically normal, particularly in the inter-ictal phase. Non-specific, non-localising oculomotor deficits have been described in VM inter-ictally, such as smooth pursuit deficits in 48% of patients, spontaneous nystagmus in 10% of patients, and central positional or gaze-evoked nystagmus in 28% of patients [32]. When present, these abnormalities are typically subtle and other central disorders should be excluded when these findings are identified. During an acute episode, spontaneous and positional nystagmus has been recorded in 70% of patients, as well as unsteadiness during the symptomatic period [33]. VM and BPPV can co-occur in the same individual, and VM can mimic BPPV where there may be recurrent episodes of positional nystagmus and vertigo that tend not to resolve with repositioning manoeuvres [34].

Investigations

There is no specific diagnostic test for VM. Vestibular function tests have shown

Table 2 Prophylactic drug therapy options for Vestibular migraine (adapted from (40))

Drug	Group	Initial dose	Target dose	Cautionary note
Amitriptyline	Tricyclic antidepressant	10-25mg daily at night	Increased in 10-25mg steps every 3-7 days in 1-2 doses until control, usual maintenance dose 25-75mg/day	Can cause drowsiness, dry mouth
Topiramate	Anticonvulsant	25mg at night for 1 week	Increased in 25mg steps at weekly intervals; usual maintenance dose 50-100mg/day in divided doses; maximum 200mg/day	Avoid in acute porphyria, risk of metabolic acidosis
Propranolol	Beta-blocker	40mg/day	80-240mg/day in divided doses	Diabetes, first-degree atrioventricular block, Asthma/COPD, myasthenia gravis, portal hypertension, psoriasis, hypotension
Pizotifen	Antihistamine	Initially 500 micrograms at night	Increase gradually to usual dose 1.5mg at night or 3 divided doses; maximum 4.5mg/day	Avoid abrupt withdrawal, history of epilepsy, closed angle glaucoma, urinary retention
Candesartan	Angiotensin receptor blocker	16mg daily	16mg daily	Aortic or mitral valve stenosis, elderly, hypertrophic cardiomyopathy, patients of black-African or African-Caribbean origin, history of angioedema, primary aldosteronism, renal artery stenosis
Venlafaxine	Serotonin and norepinephrine reuptake inhibitor (SNRI)	37.5mg/day	75-225mg/day	Caution in diabetes, heart disease (monitor blood pressure), history of bleeding disorders, epilepsy. Can cause loss of sexual desire, dry mouth, insomnia
Gabapentin	Anticonvulsants	300mg/day	1200-2400mg/day	Caution in diabetes, elderly, mixed seizures. Can cause sedation, peripheral oedema
Flunarizine (unlicensed use in UK)	Calcium Channel Blocker	5-10mg	10mg/day	Caution in heart disease, liver disease and kidney disease. Can cause weight gain, sedation, depression

a range of mild abnormalities but there are no consistent trends observed. Mild sensorineural hearing loss has been described especially affecting the lower frequencies, but in such cases Ménière's disease should be strongly suspected. Central auditory processing deficits are reported in VM with prolonged latencies on auditory brainstem response testing [35], but such findings are not specific for VM.

Management

Management of VM is based on recognised approaches for migraine. A dizziness diary can be useful in assessing an individual's response to treatment and guide the timing of preventative therapies.

Treatment for acute episode

There is no evidence-based approach for acute treatment of VM, although many specialists will advocate the use of antiemetic medication, particularly for the treatment of accompanying nausea or vomiting. Contrary to migraine, there is inconclusive evidence for triptan use in VM. Zolmitriptan has been shown to have some benefit in a small pilot randomised placebo-controlled trial [36] and Rizatriptan reduces vestibular-induced motion sickness in patients with VM [37]. Where there is an unremitting, prolonged, distressing episode of VM, treatment with intravenous methylprednisolone has been found to be effective [38].

Prophylactic treatments

A recent systematic review and meta-analysis assessing the efficacy of preventative treatments for VM identified that antiepileptic drugs, calcium channel blockers, tricyclic antidepressants, beta-blockers, serotonin and norepinephrine reuptake inhibitors, as well as vestibular rehabilitation demonstrated improvements in outcome parameters [39]. However, due to significant heterogeneity of studies and lack of standardised reporting outcomes a preferred treatment modality could not be determined. A similar conclusion was reached by another prospective multicentre study evaluating acetazolamide, amitriptyline, flunarizine, propranolol or topiramate for VM, finding all similarly reduced symptom severity and frequency [40].

A prospective randomised non-placebo-controlled trial suggested flunarizine is effective in reducing the severity and frequency of vertigo attacks in VM patients [41], with positive patient experiences [42]. Another prospective randomised trial compared the effectiveness of venlafaxine and propranolol in VM patients and found both were effective treating vertiginous symptoms, however venlafaxine was better at controlling depressive symptoms [43], as also shown in another study [44].

Dietary modification with reduction in migraine triggers may be beneficial, and lifestyle modification should be considered where other triggers such as stress and irregular sleep pattern may be contributory. Regular exercise can reduce stress and improve sleep [30] and reduce the intensity and frequency of VM [45]. Given that up to 65% of patients with VM may exhibit anxiety disorder [46] there may also be a role for cognitive behavioural therapy in these patients.

Vestibular rehabilitation is a useful non-medicinal pharmacological approach to treating VM, with a review reporting significant improvement in all outcomes measures, including headaches [47], although good quality randomised controlled trials are lacking.

Conclusion

Vestibular migraine is a common balance disorder with likely genetic, epigenetic and environmental factors contributing to its development. Diagnosis can be challenging due to symptom overlap with other disorders and lack of a specific diagnostic test. A thorough history and examination is essential together with relevant investigations to rule out other neurological or otological disorders. There is growing evidence that the shared pathophysiology involves central sensitisation, maladaptive neuroplasticity, thalamocortical dysrhythmia, abnormal sensory gating, and abnormal functional connectivity with dysmodulation of multimodal sensory processing. Life experiences may drive maladaptive neuroplasticity of large-scale networks involved in sensory, attention and emotion processing.

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Endnotes

[1] the sensation of self-motion when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement.

[2] the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion.

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Arnold's Nerve

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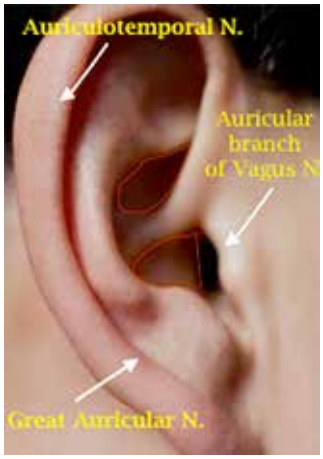

Figure 2. Nerves of the external ear

Figure 3. Friedrich Arnold. From: http://upload.wikimedia.org/wikipedia/commons/6/67/Friedrich_Arnold.jpg "The National Library of Medicine believes this item to be in the public domain."

The *auricular branch* of the vagus or Arnold's nerve is also called the Alderman's nerve. The term arose because it was alleged that voracious aldermen and their guests, during massive banquets, would scratch their outer ears to evoke vomiting [1] and thereby relieve their over-distended stomachs to permit yet further gluttony. This perhaps is the modern equivalent of the Romans' mythical visit to the vomitorium between courses.

Arnold's nerve conveys sensation from the tragus and external acoustic meatus (Figures 1 & 2). It is a mixed general somatic afferent nerve composed of vagal, glossopharyngeal, and facial nerve fibres. Confusingly, the term is also applied to the greater occipital nerve of Arnold [2]. The eponym has been associated with the related Arnold's canal – the passage in the petrous temporal bone for Arnold's nerve, and Arnold's otic ganglion.

Arnold's nerve is the remnant of the embryonic nerve that supplies the first branchial arch, which includes the external acoustic meatus, middle ear and auditory tube. The auricular nerve arises from the superior jugular ganglion of the vagus [3] and is joined by a filament from the inferior (petrous) ganglion of the glossopharyngeal (Figure 1). Crossing the temporal bone about 4mm above the stylomastoid foramen, it gives off an ascending branch that joins the facial nerve. Fibres of the nervus intermedius of Wrisberg (VII) may join the auricular nerve explaining the vesicles that sometimes accompany geniculate zoster.

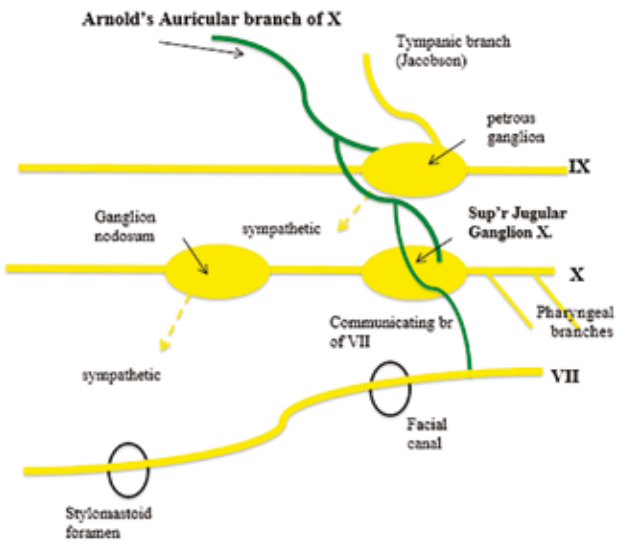

Figure 1. Diagram of Auricular branch of vagus and its communication with glossopharyngeal and facial nerves

In original studies of comparative anatomy in 1913-22 [4,5], the eminent, Glasgow Otologist Albert A Gray (1869-1936) elucidated the minutiae of anatomical detail and its variations in both man and animals, and described the 'bullar plexus'. He noted that descriptions of the course and relations of Arnold's nerve 'in standard anatomical textbooks were quite inadequate and probably incorrect.' He demonstrated:

> *….This plexus was clearly composed of branches from at least two nerves, the facial and the vagus; and probably branches from the glossopharyngeal also took part in its formation. The existence of this structure in several mammals of different orders appeared to me to indicate that it was probably represented in man, but had hitherto escaped discovery on account of the difficulties of making satisfactory dissection of that region in the human subject…*
>
> *Arnold's nerve enters the temporal bone on the external surface of the jugular fossa, and runs horizontally where a small twig unites it with the facial nerve. Turning round the posterior aspect of the facial nerve it comes to be immediately behind the chorda tympani with which it connects, then turns more abruptly downwards and leaves the bone through a small foramen close to the style-mastoid foramen…The bullar plexus indeed in the human subject consists of the communications of Arnold's nerve (the auricular branch of the vagus) with the facial nerve, and in some cases at least with the chorda tympani. [5]*

Gray stressed the differences between mammals and man in whom 'the development of the mastoid antrum and the mastoid cells compels the facial nerve to seek a more devious course [4].

Clinical

Because Arnold's nerve innervates the external auditory canal, when the canal is stimulated by scratching, the reflex vagal response is vomiting, or a cough – that is Arnold's ear-cough reflex [6]. The afferent projection from the auricular branch to the nucleus tractus solitarius connects it to the efferents in the dorsal nucleus of the vagus nerve and the nucleus ambiguus which supply inter alia the heart and lungs. Arnold's nerve has also been claimed as the basis for so-called auriculo-palatal, auriculo-lacrimal, auriculo-cardiac reflexes, which are of minor clinical significance [6].

Gupta et al. reported a survey of 500 patients that revealed a 4.2% incidence of Arnold's ear-cough reflex [6]. In another clinical survey of 688 patients an incidence of 1.74% was found, usually unilaterally, and elicited from each canal quadrant [7]. A positive reflex did not indicate any particular ear disease. Arnold's reflex has been claimed as an occasional cause of chronic cough in children and adults [8] with earwax and in those wearing hearing aids. There is however a danger of over-diagnosis of this syndrome in practice, as too easy an explanation for chronic cough which should necessitate careful investigation.

The nerve may be involved by glomus jugulare and other tumours, and by trauma involving the lateral posterior fossa and jugular canal. Autosomal dominant hereditary sensory neuropathy HSN1 can rarely present with adult onset paroxysmal cough triggered by noxious odours or by pressure in the external auditory canal (Arnold's ear-cough reflex), gastro-oesophageal reflux, a hoarse voice, cough syncope and sensorineural hearing loss [9].

Friedrich Arnold (1803–1890) (Figure 3) studied anatomy at the University of Heidelberg under Friedrich Tiedemann (1781-1861). He graduated in Medicine in September 1825. In 1834 he was appointed Extraordinary Professor, Faculty of Medicine, at Heidelberg, and in 1835 became Professor at of Anatomy at the University of Zurich.

Arnold described the external arcuate fibres (Arnold's bundle), the arcuate nuclei and the otic ganglion (Arnold's ganglion). In his *Tabulae Anatomicae quas ad Naturam Accurate Descriptas* he first depicted the frontopontine tract from the frontal cortex through the anterior limb of the internal capsule via the cerebral peduncle (Arnold's tract). Arnold himself noted the reflex cough when the external auditory meatus was stimulated.

Of many publications on microanatomy and physiology of the nervous system, his textbook, published with his brother Johann Wilhelm Arnold (1801–1873) [10], was the most respected. His *Icones nervorum capitis* (1834) [11], provided lithographic engravings of the cranial nerves showing their topography, 'with a distinctness and beauty never been seen before [12]'. He was regarded as one of the greatest dissectors of all time.

His pupils included Ludwig Edinger (1855-1918) and Hubert von Luschka (1820-1875). He moved again in 1845 to the Chair at Tübingen, and finally returned to his original Chair at Heidelberg, where he died aged 87.

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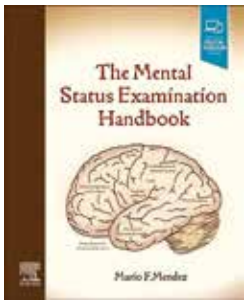
The Mental Status Examination Handbook

I came across this book by chance when browsing in the Psychiatry section of a bookshop. Based on the title one can understand why it was shelved there (although the back cover helpfully lists neurology above psychiatry in the "Recommended Shelving Classification") since, at least in the UK, mental status examination (which the author abbreviates "MSX") is a core feature of psychiatric rather than neurological practice. However, this book is essentially about cognitive examination, as one might anticipate from an author who has made significant contributions in cognitive neurology over several decades. He may be familiar as the co-author with Jeffrey Cummings of *Dementia. A clinical approach* (Butterworth-Heinemann, third edition 2003).

After some general principles and essential neuroanatomy, the core of the book is devoted to "mental status" (= cognitive) testing ordered by domain: attention, language, memory, perception, praxis, and executive abilities. The emphasis is firmly on what can be achieved in the clinic and at the bedside, rather than by formal neuropsychological assessment. In this context, I found the author's expositions on apraxia and on acalculia particularly masterful, reflecting many years of experience in assessing these constructs.

There then follows a section on cognitive scales and inventories, with brief descriptions of some of the most frequently used screeners (e.g. MMSE, MoCA), and a brief overview of what to expect from a neuropsychologist's assessment. Finally, there is a chapter on "tele-neurobehavior" (a neologism?) looking at telephone screeners, both dedicated for this purpose and adapted from existing pen-and-paper screeners, which is most welcome in light of the changes in cognitive neurology practice enforced by the COVID pandemic and which may persist into the longer term.

The only comparable book I can think of is John Hodges' *Cognitive assessment for clinicians* (sometimes colloquially known as "Hodgeography") which appeared in 3 editions published by Oxford University Press between 1994 and 2018. The Mendez book has the potential advantage of being downloadable and searchable. There are some unfortunate typos, for example diagonistic and agonistic apraxia is garbled into "diagnostic and agnostic" (P128 and Index), although in the lengthy appendix which summarises mental status tasks this error is avoided (P235). My copious annotations suggest that the index is not adequate. Nevertheless, this is a very worthy volume which can be enthusiastically recommended for those beginning or refreshing their clinical skills in cognitive neurology.



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UKABIF Annual Conference 2021

Conference details: 8 November, 2021, Royal Society of Medicine, London, UK and streamed virtually. ***Report by:*** Louise Blakeborough, MSc on behalf of UKABIF. ***Conflict of interest statement:*** None declared. ***Published online:*** 14/4/2022.

UKABIF's Annual Summit took place at London's Royal Society of Medicine. The meeting updated delegates on the recent progress following the publication of the 'Acquired Brain Injury and Neurorehabilitation: Time for Change' report, as well as discussing the developments and improvements in the delivery of care for people with Acquired Brain Injury (ABI).

Professor Andrew Bateman, UKABIF Chair, welcomed delegates and introduced Chris Bryant, Labour Member of Parliament for the Rhondda, and Chair of the All-Party Parliamentary Group on ABI. Chris briefed delegates on the ABI Bill which was debated in the House of Commons on the 3rd December and encouraged everyone to write to their MPs and request support for the Bill.

Leigh Day sponsored the first session on women, brain injury and sport, currently a 'hot' topic with research demonstrating the differences in the way women and men experience sport-related brain injury and neurodegeneration. Freya Holdaway, a professional footballer, described how three concussions in 18 months resulted in her retirement from the game. Dr Elisabeth Williams, Senior Lecturer in Applied Biomechanics at Swansea University highlighted the sex differences in sports players and emphasised the need for female-orientated pitch protocols to deal with concussions, and for treatment to be tailored differently.

The second session was sponsored by Cygnet Health Care, looking at ways to improve clinical practice for people with brain injury. Dr Tony Perini, Consultant Neuropsychiatrist and Alex Scordis-Hutchinson, Neuro-Occupational Therapist, both from Cygnet Health Care, discussed how brain injury and mental health continue to be boxed separately but require a holistic approach to maximise outcomes. "Neurologic Music Therapy (NMT) has a unique contribution to rehabilitation" said Elizabeth Nightingale, Neuro Services Lead and Trainer Neurologic Music Therapist, Chiltern Music who discussed a NMT pilot clinic being run by a partnership between Chiltern Music Therapy and the Regional Neurological Rehabilitation Unit (RNRU) at Homerton Hospital. Chiltern Music Therapy uses NMT techniques to support patients to meet their rehabilitation goals in the functional domains of speech and language, sensorimotor, and cognitive skills.

"We need to look beyond the traditional multidisciplinary team to the work of the 'hotel service staff' in neurological care homes" said Dr Julie Latchem-Hastings, Research Fellow at Cardiff University after observing the interactions of staff with residents. She said: "All these staff help towards the rehabilitation of patients but go unnoticed, untrained and are not an accepted part of the team".

UKABIF Group.

Speaker – Sara Hazzard.

The session sponsored by Neuro ProActive looked at the explosion of neurotechnology developments with a panel comprising Liz Ashall-Payne, ORCHA, Rachel Taylor, Operational Manager, South Wales Trauma Network and Dr Sally Lewis, National Clinical Lead for Value-Based and Prudent Healthcare and Honorary Professor at Swansea School of Medicine. They discussed setting standards in digital technology, developing an interactive patient information system and the footprint for fully integrated systems.

Driving change was the theme of the final session, sponsored by Irwin Mitchell Solicitors. Improving the return to education (RTE) after brain injury was discussed by Lisa Turan, Chief Executive Officer, The Child Brain Injury Trust and Dr Gemma Costello, Head of Psychosocial Services, The Children's Trust, on behalf of the National ABI in Learning and Education Syndicate (N-ABLES). They described projects aimed at supporting a child's RTE including an N-ABLES initiative comprising a booklet and poster 'ABI Return – Children and Young People with Acquired Brain Injury – guiding their return to education' to help all those involved to prepare for, and achieve, a successful return and progress their recovery. A copy of the booklet and poster is available from www.ukabif.org.uk/.

An expert-led, integrated care pathway was described by Dr Peter Jenkins, Consultant Neurologist, Southampton Hospital. It is being developed to deliver accurate and timely diagnosis and optimal treatment at all stages during a TBI patient's care. The pathway proposes a specialist interdisciplinary TBI team, led by a neurosciences-trained brain injury Consultant. The Chartered Society of Physiotherapy (CSP) has been driving a campaign to improve access to rehabilitation services across the UK involving over 50 national bodies and charities. Sara Hazzard, Assistant Director of Strategic Communications, CSP said: "This is not too big a problem to change, but it is too important to ignore".

James Piercy, the conference afternoon Chair thanked all the speakers, delegates, sponsors, exhibitors, and remote audience and concluded by saying: "Please back the ABI Bill – write to your MP".

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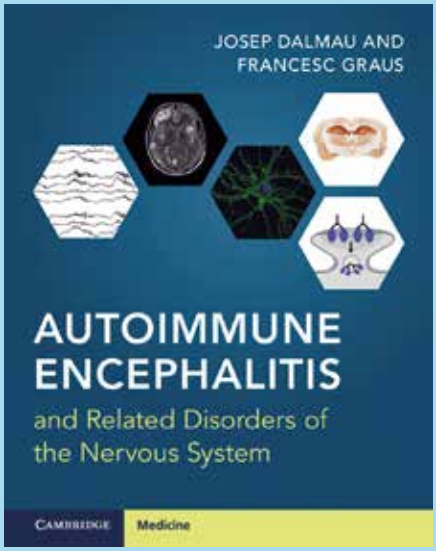

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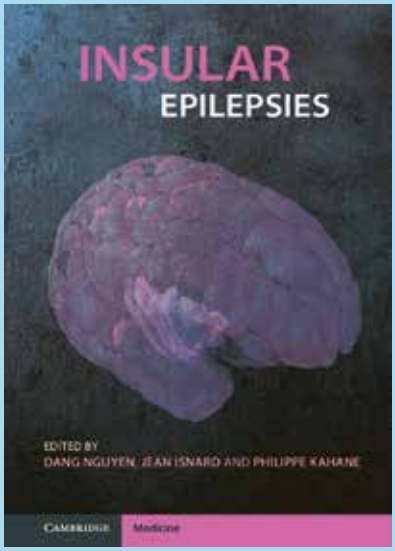

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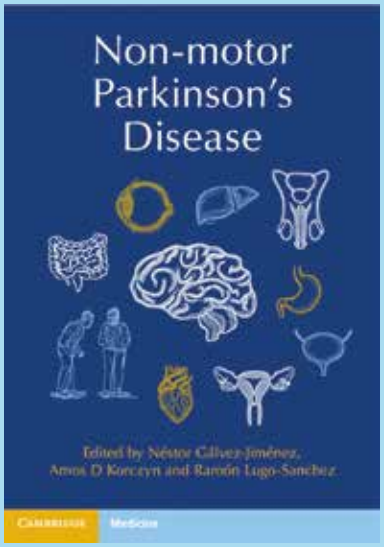

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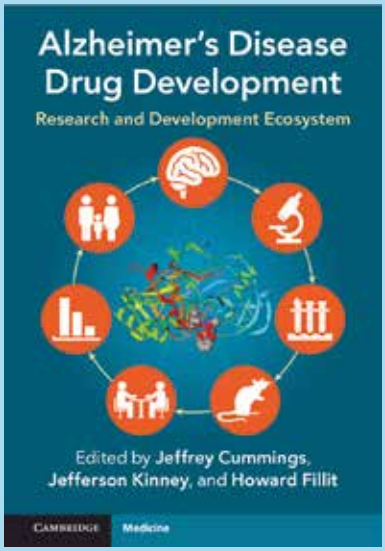

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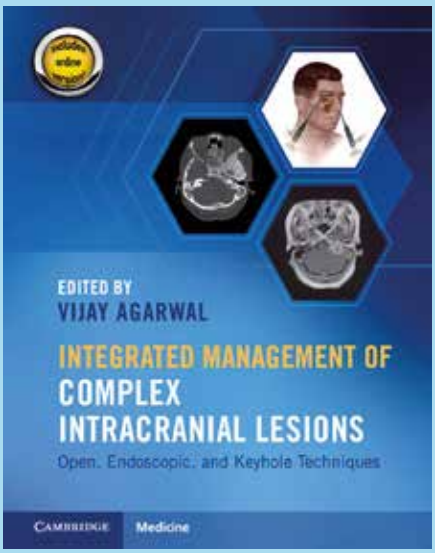

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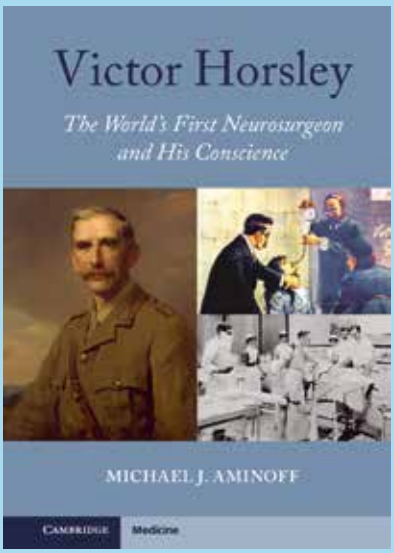

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Social Determinants of Neurological Disease: Tackling Inequalities

Conference details: 25 November, 2021, Queen Mary University, London, UK. ***Report by:*** Christina Mousele, Alastair J Noyce, Ruth Dobson and Charles R Marshall, Barts Health NHS Trust, London, UK. ***Conflict of interest statement:*** None declared. ***Published online:*** 19/4/2022.

Synopsis

Social Determinants of Neurological Disease: Tackling Inequalities was held at the Preventive Neurology Unit at Queen Mary University of London on the 25th of November 2021. The symposium brought together researchers and healthcare professionals with an interest in the influence of social determinants on health outcomes. In a varied programme that included lectures and panel discussions, the event addressed knowledge gaps in the understanding of social determinants of neurological diseases, and highlighted lessons that can be learned from progress in addressing these factors in other disease areas.

Opening the meeting, Dr Ruth Dobson introduced data showing a higher risk of multiple sclerosis in Black, Asian and ethnic minorities (BAME), which is more likely associated with the higher prevalence of recognised social risk factors for multiple sclerosis, such as smoking status, across these groups [1]. She also presented data showing that a large number of excess dementia deaths in England and Wales are attributable to socioeconomic deprivation. Social determinants of health include non-medical factors that influence health outcomes, including educational level, poverty, geography, race and gender and Dr Dobson suggested that the symposium should prompt delegates to consider how inequalities in healthcare might manifest from a research perspective, including access to research for potential participants, questions about study results that are truly representative of the population and subsequent influences on clinical care.

The first half of the symposium focused on lessons that can be learnt from other diseases, including HIV and cancer screening. In this context, Dr Vanessa Apea (Barts Health NHS Trust) presented data from HIV research demonstrating an increased rate of late diagnosis of HIV infection in women, older age groups (aged 50+), people of Black African ethnicity and transgender individuals [2]. She then focused on how patient-centred care is the key in terms of moving past this injustice towards agency. Advocacy, active inclusion of all voices, active listening, using culturally appropriate resources and psychologically safe spaces, and ensuring health and research literacy could all help to engender agency. Dr Apea also touched on the matter of racism as a force determining the life of individuals from minority ethnic backgrounds and influencing the distribution of social determinants of health, and concluded that routinely monitoring for differential exposures, opportunities, and outcomes by race, exploring lived experiences and intersectional systems of discrimination, and ensuring diverse representation in research is crucial to tackle racism as a silent perpetuator of health inequalities [3].

Following Dr Apea's lecture, Dr Samantha Quaife (Queen Mary University of London) described how socioeconomic inequalities lead to a disproportionate cancer burden among those who are more deprived, with socioeconomic gradients in cancer screening uptake exacerbating this discrepancy. Dr Quaife then expanded on behavioural science approaches that can be implemented to mitigate this problem, with particular emphasis on the social ecological model [3]. This argues that the only way to fully and holistically understand a problem is by comprehending the different levels or parts that constitute it. These include public policies, community factors, organisational, interpersonal and individual parameters. Focusing on what can be changed on an individual level, Dr Quaife presented the COM-B model, which proposes that there are three components to any behaviour (B): Capability (C), Opportunity (O) and Motivation (M). In order to perform a particular behaviour, one must feel that they are both psychologically and physically able to do so (C), have the social and physical opportunity for the behaviour (O), and want or need to carry out the behaviour more than other competing behaviours (M) [4]. As each of these components interact, interventions must target one or more of these in order to deliver and maintain effective behavioural change. Dr Quaife explained useful methods to target capability and opportunity in the field of cancer screening which can also be applied in the field of preventive neurology. These could include advanced notification and public campaigns to increase awareness of the importance and availability of disease screening, tailored communication to promote engagement with the screening scheme, as well as regular reminders, timed appointments, and use of simple tests to then facilitate compliance with lifelong screening [5].

Professor Carol Rivas (University College London) subsequently gave a comprehensive talk on the impact of intersectionalities on the care of people with chronic diseases. She defined health inequalities as systematic differences in the health of people occupying unequal positions in society [6]. She emphasised that multiple structural, contextual and individual factors determine social disadvantage and influence health experience, and their effect is not simply additive. None of these factors is a stand-in for any other and they are all necessary in generating adequate depictions of social inequalities in healthcare. In other words, social determinants of health intersect to create a mutually constituted vulnerability [7,8]. This stresses the need for an intersectional lens to be applied. Without this intersectional lens, important information may be obscured. Intersectionality can be divided into categories, including intra-categorical, whose aim is to make visible previously invisible group dynamics created by the perception of thinking of a group category as homogeneous; anti-categorical, which challenges intersectional relationships and notions of identity as fixed; and inter-categorical, which provisionally adopts existing analytical categories to document relationships of inequality [9]. To tackle ethnocentric determinants of healthcare inequalities, requires a rich longitudinal intersectional understanding of experiences of people from minorities and with chronic conditions or disabilities, and a focus on ensuring easy access to networks of emotional and practical support, health and social care, as well as vital resources, such as medicine and food. Specific attention was given to the role that lay co-researchers can play in understanding, inspiring trust and maintaining communication with study participants from different ethnic groups.

Following these talks, Dr Andrew Singleton (National Institutes of Health, USA) pointed to knowledge gaps in common neurological diseases due to a failure to reflect in research the diversity of people suffering from these diseases. This issue mainly arises from the traditional perception that disease entities are monolithic, thus limiting the importance of diversifying the basis of our understanding of disease. Collecting data from those who are already embedded in or readily available to the research pipeline is easier for researchers. However, unequal representation in research is not only a socially unfair phenomenon, but also a scientifically inefficient way to address global diseases. Differences in disease biology and genetics between demographic groups have the potential to deliver important insights into aetiology and treatment of neurological diseases. To address these problems the current focus should be on diversifying research. However, engaging new communities to research, both as study participants, but also as researchers executing the work, is challenging and requires new or modified infrastructure, and a commitment from funders to support efforts outside of the norm. Dr Singleton ended his talk by emphasising that the efforts towards diversification of research should target multiple levels, including genetics, genomics, biomarkers, clinical features, treatment response, disease pathology and cellular models.

The symposium raised important issues for clinicians and researchers working in the field of neurological disease. While there is evidence to show that the burden of major neurological

diseases varies according to social factors such as ethnicity and socioeconomic status, these have largely been neglected in research and in the clinic. Progress in other common diseases provides a roadmap for us to begin to address this knowledge gap so that we can deliver representative translational research and effective clinical care across social, cultural and geographical boundaries.

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The 20th Annual King's Neuromuscular Symposium

Conference details: 28 January, 2022. Conference streamed virtually. ***Report by:*** Giulia Attard Navarro and Charles Fry, Neurophysiology Registrars at King's College London, UK. ***Conflict of interest statement:*** None declared. ***Published online:*** 28/4/2022.

The 20th Annual King's Neuromuscular symposium, held online for the second consecutive year, hosted speakers from Australia, UK, Netherlands, France, and the USA. The meeting provides practical clinical updates and interesting cases for healthcare professionals who look after patients with neuromuscular diseases. This was our third attendance and, as previously, we left with useful tips that we have used almost immediately afterwards.

The symposium started with Professor Matthew Kiernan delivering a fascinating talk on nerve excitability studies. Neurophysiology training in the UK does not typically include threshold tracking so it was interesting to discover how this technique has improved our understanding of uraemic and chemotherapy-induced neuropathies, its role in monitoring response to treatments, and how it may detect abnormalities earlier than nerve conduction studies. It must indeed be an excellent talk when Richard Hughes writes, "excellent talk" in the chat of the Richard Hughes lecture!

Our in-house peripheral nerve expert, Dr Rob Hadden (Consultant Neurologist, King's College Hospital, UK) delivered the second talk. He gave a clear explanation of the recently updated (2021) CIDP guidelines, which he co-authored. The guidelines now include helpful flowcharts for navigating this complicated disease. He made three important points: CIDP remains a diagnostic challenge, refractory CIDP may be the wrong diagnosis (test those nodal/paranodal antibodies!) and CIDP variants are the most likely to be mis-diagnosed. The guidelines provide important red flags, centred around these variant forms. Guillain-Barré syndrome guidelines are also in the pipeline and a CIDP guidelines phone app is under development.

We stayed on the CIDP theme, but headed to the Netherlands for a talk by Dr Franssen with practical tips on interpreting nerve conduction studies in CIDP. He nicely described the key terms (including CMAP drop, conduction block, temporal dispersion) and the origins of cut-off values for velocity and amplitude or area changes dating back to the late 1970s. He finished with 6 practical hints emphasising the importance of limb temperature, stimulator position, assessing the shape of the CMAP not just its amplitude, and interpreting with caution when CMAPs are small (<1mV).

Dr Paul Seror, Consultant Rheumatologist from Université Paris VI, France, gave an in-depth and highly practical talk on neuromuscular disorders affecting the scapula, of interest to a diverse multi-disciplinary audience. He showed us a systematic approach to clinical examination and electrophysiology of the muscles that control the scapula, including video analysis of the scapular rhythm during upper limb circumduction. Video analysis is something we may incorporate into our own clinics as the ability to pause and replay can be extremely helpful. A thorough electrodiagnostic study further improves the diagnosis.

If, like us, you rarely come across mitochondrial diseases then Dr Pitceathly's talk from University College London, UK, would have been ideal for you. There have been rapid developments in this field, which he managed to cover along with the common presentations and the basics of mitochondrial genetics. It was fantastic to hear that at Queen Square the 100K genomes project resulted in new genetic diagnoses in 30% of patients. There are, however, many ongoing diagnostic challenges including heteroplasmy, complex family histories and phenocopies.

Professor Charles Thornton from Rochester, USA, gave us an excellent update on the clinical and pathological features of myotonic dystrophy, including some very helpful videos of myotonia. He reminded us that myotonic dystrophy is a heterogeneous disorder with many unanswered questions and considerable scope for research. Nevertheless, he shared exciting developments in treatment of this disease. The first pre-clinical trial of an antisense oligonucleotide in a mouse model of myotonic dystrophy is underway, and preliminary data suggest that both the clinical myotonia and RNA toxicity are improved.

Finally, Professor Roy Freeman treated us to a very informative and entertaining talk about some of the many faces of autonomic neuropathy. He navigated the complex topic of autonomic neuropathies and provided useful tips on how to approach these disorders. We mention here two of the important points he made. When suspecting an autonomic neuropathy, nicotinic acetylcholine receptor should always be requested because autoimmune autonomic ganglionopathy is treatable. Treatment-related neuropathy, should be suspected in diabetic patients who develop acute severe pain and dysautonomia after rapid correction of blood glucose. The hallmark of this condition is a rapidly declining HbA1c.

Key learning points:

1. Nerve excitability studies detect abnormalities earlier than nerve conduction studies in some neuropathies such as uraemic and oxaliplatin induced neuropathies.
2. New chronic inflammatory demyelinating polyneuropathy (CIDP) guidelines simplify this complex diagnosis.
3. In CIDP interpreting nerve conduction slowing and amplitude drops requires careful attention to limb temperature, stimulator position, CMAP duration and CMAP area.
4. In scapular winging, both video and electrophysiology contribute to accurate diagnosis.
5. Whole genome sequencing has resulted in a new diagnosis in 30% of patients with previously undiagnosed mitochondrial disorders.
6. Gene therapy is promising in the management of myotonic dystrophy.
7. There are important treatable and reversible causes of autonomic neuropathy.

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The Royal Marsden Upcoming Events

Senior Adult Oncology Study Day (In-Person)
Monday 20th June 2022

Care of the Patient with Prostate Cancer Study Day (In-Person)
Monday 27th June 2022

Children and Young Adult Neuro-oncology Study Day for Paediatric Nurses (In-Person)
Thursday 29th September 2022

The Management of Low-Grade Gliomas Conference (In-Person)
Thursday 20th October 2022

Adult Palliative Care (Virtual) Study Day
2nd & 3rd November 2022

The 13th Annual Royal Marsden Head & Neck Conference (In-Person)
Friday 11th November 2022

The Royal Marsden Haemato-Oncology Study Day (In-Person)
Monday 14th November 2022

The 15th Royal Marsden Opioid, Cannabinoid and Gabapentinoids Conference (In-Person)
24th & 25th November 2022

The Royal Marsden Interventional Approaches for Cancer related Pain and Acute Pain & Persistent Post Surgical Pain Conference (In-Person)
15th & 16th December 2022

Exercise and Cancer Study Day (In-Person)
Wednesday 22nd February 2023

Managing Brain Metastases in 21st Century Conference (In-Person)
Thursday 9th March 2023

Imaging: Radiology in Cancer Diagnosis & Management (In-Person)
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