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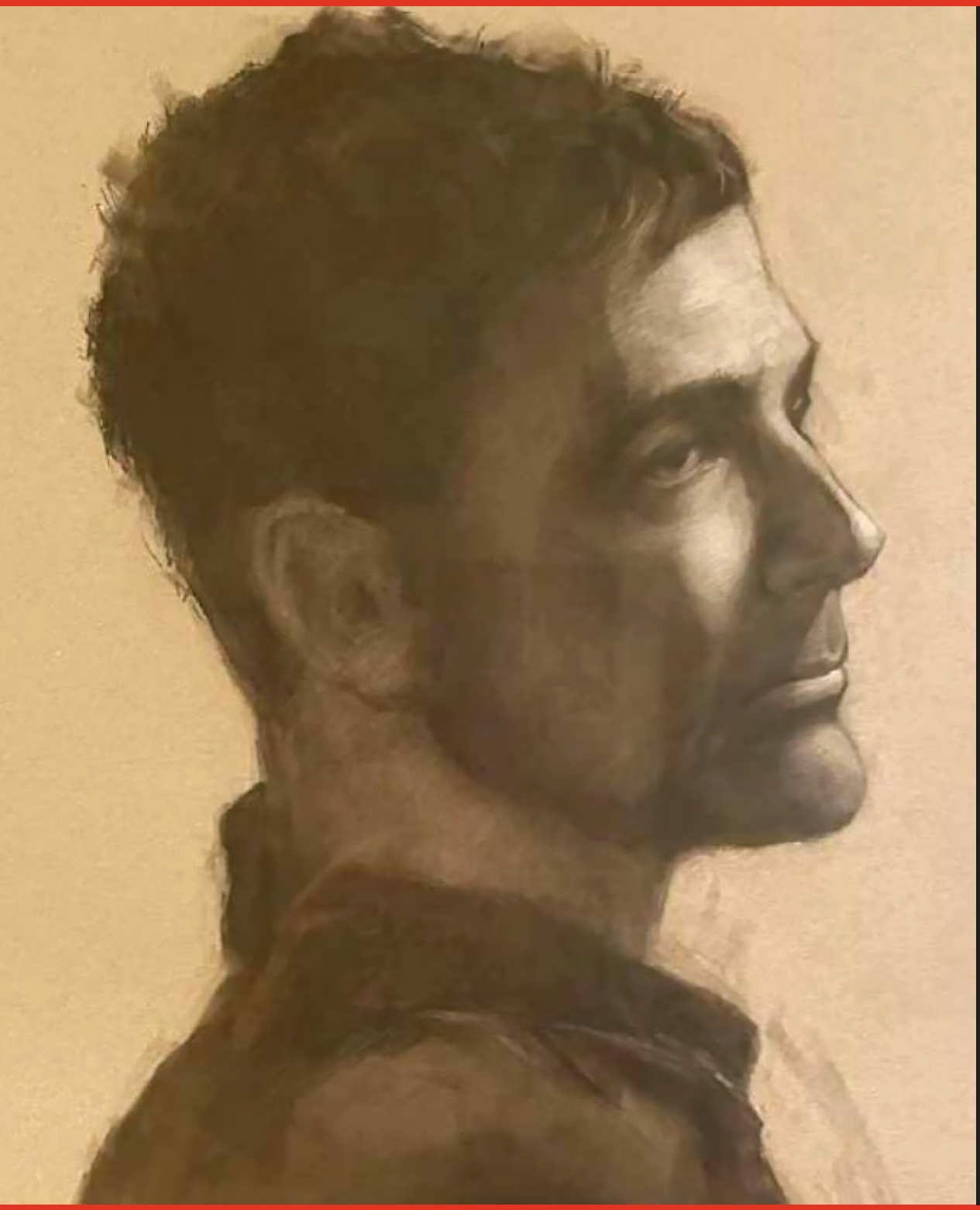
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

SLOW DOWN SPMS WITH ACTIVE DISEASE. IT'S TIME FOR MAYZENT®.

MAYZENT is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.[1]

Scan here to learn more about:

Useful resources to support you and your SPMS patients

A useful guide with a list of medicines that can interact with CYP pathway and potential limitations to be used concomitantly with MAYZENT

How to switch patients to MAYZENT from other disease modifying treatments

1. Mayzent® (siponimod) Summary of Product Characteristics. Novartis.

Prescribing information and adverse event reporting can be found on the opposite page

NOVARTIS

UK | July 2021 | 137609

Prescribing Information: Mayzent® ▼ (siponimod)

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).

Presentation: Film-coated tablets containing 0.25 mg or 2 mg siponimod (as siponimod fumaric acid).

Indication: Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

Dosage and administration: Treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Before treatment initiation, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. In patients with a CYP2C9*3*3 genotype, siponimod should not be used. In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily. The recommended maintenance dose of siponimod in all other CYP2C9 genotype patients is 2 mg. Siponimod is taken orally once daily, with or without food and should be swallowed whole with water. Treatment initiates with a titration pack that lasts for 5 days, the patient's prescribed maintenance dose of siponimod is reached on day 6. During the first 6 days of treatment, if a titration dose is missed on one day treatment needs to be re initiated with a new titration pack. If a dose is missed after day 6, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled. If maintenance treatment is interrupted for ≥4 consecutive daily doses, siponimod needs to be re initiated with a new titration pack. Siponimod should be used with caution in patients aged ≥ 65 years due to insufficient data on safety and efficacy. No dose adjustment is needed in patients with renal impairment. Siponimod must not be used in patients with severe hepatic impairment (Child Pugh class C). Caution should be exercised when initiating treatment in patients with mild or moderate hepatic impairment, no dose adjustment is needed.

Contraindications: Hypersensitivity to the active substance, or to peanut, soya or any of the excipients. Immunodeficiency syndrome. History of progressive multifocal leukoencephalopathy or cryptococcal meningitis. Active malignancies. Severe liver impairment (Child-Pugh class C). Patients who in the previous 6 months had a myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure. Patients with a history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker. Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser). During pregnancy and in women of childbearing potential not using effective contraception.

Warnings/Precautions: Siponimod is not recommended in patients with: Severe cardiac arrhythmias requiring Class Ia (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic drugs, calcium channel blockers (e.g. verapamil, diltiazem) and other medications (e.g. ivabradine or digoxin) which are known to decrease the heart rate (HR). A history of symptomatic bradycardia or recurrent syncope, uncontrolled hypertension, or severe untreated sleep apnoea. QTc prolongation >500 msec. *Infections*: Siponimod reduces the peripheral lymphocyte count to 20-30% of baseline and may increase the risk of infections. Before initiating treatment, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are recommended periodically during treatment. Confirmed absolute lymphocyte counts <0.2 x 10^9/l, leads to dose reduction to 1 mg, or interruption of supply in patients already receiving 1 mg. A case of cryptococcal meningitis (CM) has been reported for siponimod. Siponimod should be suspended in patients with symptoms consistent with CM until CM has been excluded. Initiate appropriate treatment if CM is diagnosed. No cases of progressive multifocal leukoencephalopathy (PML) have been reported. Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML, if suspected, treatment should be suspended. Cases of herpes viral infection have been reported in the development programme. Patients without a physician-confirmed history of varicella zoster virus (VZV) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before starting siponimod. A full course of vaccination with varicella vaccine is recommended for antibody-negative patients prior to commencing treatment. Initiation of treatment should be postponed for 1 month to allow full effect of vaccination to occur. The use of live attenuated vaccines should be avoided while patients are taking siponimod and for 4 weeks after stopping treatment. Vaccinations may be less effective if administered during siponimod treatment. Discontinuation of treatment 1 week prior to planned vaccination until 4 weeks after is recommended. The possible return of disease activity should be considered when stopping siponimod. Anti-neoplastic, immune-modulating or immunosuppressive therapies should be co-administered with caution due to the risk of additive immune system effects. *Macular oedema:* Macular oedema was more frequently reported with siponimod than with placebo in the clinical study. An ophthalmological evaluation is recommended 3-4 months after treatment initiation. Patients should report visual disturbances while on siponimod and an evaluation of the fundus, including the macula, is recommended. Siponimod should not be initiated in patients with macular oedema until resolution. Caution should be used in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in risk of macular oedema. Ophthalmological evaluation prior to initiating therapy and regularly while receiving siponimod therapy is recommended for these patients. Siponimod should be discontinued if a patient develops macular oedema. *Bradyarrhythmia:* Initiation of siponimod results in a transient decrease in HR, and a titration scheme to reach the maintenance dose on day 6 is applied at the start of treatment. HR decrease starts within one hour of first dose and the day 1 decline is maximal at approximately 3 to 4 hours (average 5 to 6 bpm). Further HR decreases upon up-titration are seen, with maximal decrease reached on day 5 to 6. With continued dosing HR starts increasing after day 6 and reaches placebo levels within 10 days after initiation. HR below 40 bpm were rarely observed. Patients who experienced bradycardia were generally asymptomatic. The decrease in HR induced by siponimod can be reversed by parenteral doses of atropine or isoprenaline. Treatment initiation has been associated with transient atrioventricular conduction delays manifesting in most cases as first-degree atrioventricular (AV) blocks. Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed at treatment initiation in >1.7% of patients in clinical studies. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours and did not require discontinuation of siponimod. Patients with the following cardiac conditions should be observed for 6 hours after the first dose of siponimod for signs and symptoms of bradycardia: sinus bradycardia (HR <55 bpm), history of first- or second-degree [Mobitz type I] AV block, history of myocardial infarction, or history of heart failure (patients with NYHA class I and II). In these patients, it is recommended that an electrocardiogram (ECG) is obtained prior to dosing and at the end of the observation period. If post-dose bradyarrhythmia or conduction-related symptoms occur or if ECG 6 hours post-dose shows new onset second-degree or higher AV block or QTc ≥500 msec, appropriate management should be initiated and observation continued until the symptoms/findings have resolved. If pharmacological treatment is required, monitoring should be continued overnight and 6-hour monitoring should be repeated after the second dose. If siponimod is considered in patients with pre-existing significant QT prolongation or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties, advice from a cardiologist should be sought prior to initiation in order to determine the most appropriate monitoring strategy during treatment initiation. If concomitant treatment is considered during initiation of siponimod, advice from a cardiologist should be sought regarding the switch to a non-heart-rate-lowering medicinal product or appropriate monitoring for treatment initiation. Bradyarrhythmic effects are more pronounced when siponimod is added to beta-blocker therapy. For patients receiving a stable dose of beta blocker, the resting HR should be considered before introducing treatment (>50 bpm siponimod can be introduced, if resting HR is ≤50 bpm, then beta-blocker treatment should be interrupted until the baseline HR is >50 bpm). Following siponimod initiation treatment with beta blocker can be re-initiated after up-titration to maintenance dose. *Liver function:* Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiating siponimod. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked. Discontinue siponimod if significant liver injury is confirmed. Caution should be exercised in patients with a history of significant liver disease. *Cutaneous neoplasms:* In clinical studies, basal cell carcinoma was the most common neoplasm reported with a similar incidence in the siponimod 2 mg and placebo groups. Additional cases have been reported with longer exposure to siponimod. Other skin malignancies, including melanoma, have been reported in patients treated with siponimod and in patients on long-term therapy with another S1P modulator. Skin examination is recommended for all patients at treatment initiation, and then every 6 to12 months taking into consideration clinical judgement. Patients treated with siponimod should be advised to promptly report any suspicious skin lesions and cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. *Unexpected neurological or psychiatric symptoms/signs:* Rare cases of posterior reversible encephalopathy syndrome have been reported for another S1P modulator but not for siponimod.Should a patient on siponimod develop any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration, a complete physical and neurological examination should promptly be scheduled and MRI should be considered. *Prior treatment with immunosuppressive or immune-modulating therapies:* When switching from other disease-modifying therapies, the half-life and mode of action of the other therapy must be considered. A CBC is recommended prior to initiating siponimod to ensure that immune effects of the previous therapy have resolved. Initiating siponimod after alemtuzumab is not recommended due to the characteristics and duration of alemtuzumab immune suppressive effects. Siponimod can generally be started immediately after discontinuation of beta interferon or glatiramer acetate. *Blood pressure effects:* Special care is indicated if patients with uncontrolled hypertension are treated with siponimod. Hypertension was more frequently reported in patients on siponimod than placebo in the clinical study. Blood pressure should be regularly monitored during treatment. *Women of childbearing potential:* Before initiation of treatment, women of childbearing potential must be informed of the risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for at least 10 days after treatment discontinuation. *Stopping therapy:* Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. Siponimod remains in the blood for up to 10 days after discontinuation and the possibility of severe exacerbation of disease after stopping siponimod should be considered. In 90% of SPMS patients, lymphocyte counts return to the normal range within 10 days of stopping therapy. Residual pharmacodynamic effects may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system and therefore caution should be exercised for 3 to 4 weeks after the last dose. *Interference with haematological testing:* Siponimod reduces blood lymphocyte counts, therefore peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a treated patient.

Interactions: Caution should be exercised during concomitant administration with antineoplastic, immune-modulating or immunosuppressive therapies, and in the weeks after administration of any of these medicinal products is stopped, due to the risk of additive immune effects. Due to additive effects on heart rate siponimod should not be concomitantly used in patients receiving class Ia or class III anti-arrhythmic medicinal products, QT-prolonging medicinal products with known arrhythmogenic properties, heart-rate-lowering calcium channel blockers or other substances that may decrease heart rate. Vaccinations may be less effective during and for up to 4 weeks after treatment. Avoid use of live attenuated vaccines due to infection risk. Siponimod is metabolised primarily by cytochrome P450 2C9 (CYP2C9) (79.3%) and to a lesser extent by cytochrome P450 3A4 (CYP3A4) (18.5%). Concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended due to a significant increase in siponimod exposure. Siponimod may be combined with most types of CYP2C9 and CYP3A4 inducers. Due to an expected reduction in siponimod exposure, the appropriateness and possible benefit of the treatment should be considered when siponimod is combined with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype, and with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype. No interaction has been observed with ethinylestradiol and levonorgestrel oral contraceptives when co-administered with siponimod.

Fertility, pregnancy and lactation: Siponimod is contraindicated in women of childbearing potential not using effective contraception. Siponimod should not be used during breast-feeding. The effect of siponimod on human fertility has not been evaluated.

Driving and using machines: Siponimod has no or negligible influence on the ability to drive and use machines. Dizziness may occasionally occur when initiating therapy, therefore patients should not drive or use machines during the first day of treatment.

Undesirable effects: Very common (≥1/10): headache, hypertension, liver function test increased. Common (≥1/100 to <1/10): herpes zoster, melanocytic naevus, basal cell carcinoma, lymphopenia, dizziness, seizure, tremor, macular oedema, bradycardia, atrioventricular block (first and second degree), nausea, diarrhoea, pain in extremity, oedema peripheral, asthenia, pulmonary function test decreased. *Other Adverse Effects:* Please consult the SmPC for a detailed listing of all adverse events.

Legal classification: POM

Marketing Authorisation (MA) number, quantities and price: EU/1/19/1414/001 Titration pack of Mayzent 0.25 mg containing 12 film-coated tablets in PA/alu/PVC/alu blister in wallet: £293.52; EU/1/19/1414/002 Pack of Mayzent 0.25 mg containing 120 film-coated tablets in PA/alu/PVC/alu blisters: £1761.12; EU/1/19/1414/003 Pack of Mayzent 2 mg containing 28 film-coated tablets in PA/alu/PVC/alu blisters: £1643.72.

Date of last revision of prescribing information: January 2021

Full Prescribing Information available from: Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Tel: (01276) 692255.

UK | January 2021 | 104386

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.report.novartis.com

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

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SPECIAL FEATURES

REGULARS

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Ann Donnelly, Co-Editor.

Happy New Year. I would like to begin by thanking you, our readers. ACNR is for you, and we welcome your contributions and feedback. You can find us on Twitter, and on Instagram, and our new website has just launched.

We have a number of ongoing series from different academic groups, and I would like to highlight the contributions from the Centre for Neurorehabilitation at UCL, led by Professor Nick Ward, who have provided us with range of insightful and influential articles over the last few years, and will continue to do for the foreseeable future. In this issue, the group look at the importance of adapting healthcare communication for patients with aphasia (Grobler et al). This article is complimented by an article from Anthony Pak-Hin Kong, in Hong Kong, who specifically looks at healthcare communication about COVID-19 for patients with aphasia.

Dr Flavia Massey, UCL, reviews in detail the current evidence for an autoimmune basis to the inflammatory manifestations (ADEM and GBS) in patients infected with COVID-19.

Thinking of a more holistic approach to healthcare, dietary restriction has produced optimistic results in early trials in patients with multiple sclerosis (Piccio et al), with relatively simple interventions such as intermittent fasting. This is something which could easily influence our clinical practice.

JMS Pearce takes an intriguing look at the historical basis of quinine in the treatment of cerebral malaria, and Dr Larner discusses the literary approach to the patient with headache, as well as providing a bracing book review. There are more book reviews and also conference reports including a review of the World Congress of Neurology.

We hope you enjoy this issue, and look forward to meeting some of you in the year ahead.

Ann Donnelly, Co-Editor
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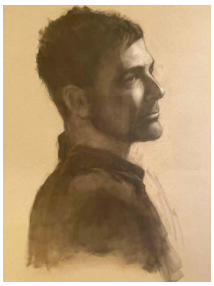
Brilliance! – A Virtual Exhibition of Creative Works from the Global Brain Tumour Community



The International Brain Tumour Alliance has launched its first virtual art exhibition of creative works from the global brain tumour community. Brain tumour patients, family members and healthcare professionals from around the world were invited to submit up to three created pieces to "Brilliance!" together with a short explanatory text describing their artworks and how they, themselves, have been affected by a brain tumour. In response to this invitation, IBTA received a large number of incredible creations which shine a light on the uniqueness of the international brain tumour community and reflect a broad range of artistic media, cultures and geographic regions. The "Brilliance!" catalogue will remain available online for viewing indefinitely as a tribute to the determination and resilience of the international brain tumour community and a symbol of hope and inspiration for all.

Our cover image shows "Jack" by Rosemary Cashman, a Canadian Nurse Practitioner in Neurooncology. Ms Cashman's portrait of "Jack" is one of the many amazing artworks which were submitted to "Brilliance!" this year. View all the artworks in a virtual catalogue at https://issuu.com/ibta-org/docs/ibta_brilliance_catalogue

Eileen Liao, BSc Hons,

completed her honours thesis in the laboratory of Dr Laura Piccio on the effects of high-fibre diet in combination with intermittent fasting in the experimental autoimmune encephalomyelitis model of multiple sclerosis. She will be entering the Doctor of Medicine programme at the University of Sydney, Australia, commencing in 2022.

Laura Ghezzi, MD,

is a Neurologist with a strong research interest in understanding inflammatory and immune-mediated mechanisms involved in the pathogenesis of multiple sclerosis (MS). She completed her medical degree and neurology residency at the University of Milan, Italy. In 2015, during her residency, she joined the group of Dr Laura Piccio at Washington University in St Louis, USA, where she spent 18 months performing research on the effects of intermittent fasting in preclinical MS models and in people with MS. During this period, she developed her passion for Neuroimmunology. In 2019, she went back to Washington University as a post-doctoral fellow in the Neurology Department supported by a fellowship from Fondazione Italiana Sclerosi Multipla (FISM). In 2020, she was awarded a three-year post-doctoral fellowship from the National MS Society to work on a project focused on mucosal associated invariant T cells in MS.

Laura Piccio, MD, PhD,

is a Clinician Scientist with research interests in integrating clinical and research aspects related to neuroinflammation in multiple sclerosis and other neurological diseases. One of her major areas of study is the complex interaction between diet, the immune system and metabolism in multiple sclerosis and its animal models. She completed her medical degree and neurology residency at the University of Milan, Italy. Then, she was awarded a post-doctoral fellowship during which she worked under the mentorship of Dr Anne H Cross at Washington University in St Louis, USA. She was then awarded the Harry Weaver Neuroscience Scholar Award from the NMSS that she completed while being a faculty member in the Department of Neurology at Washington University in St Louis, USA. Dr Piccio has published over 70 peer-reviewed articles in international journals. In February 2019, she joined the University of Sydney, Australia, as an Associate Professor at the Brain and Mind Centre. She has a dual appointment at Washington University in St Louis, USA.

Dietary restriction in multiple sclerosis: evidence from preclinical and clinical studies

Abstract

Dietary restriction (DR) interventions, which encompass both chronic and intermittent reductions in energy intake, are emerging as potential therapeutic approaches for dampening neuroinflammation and demyelination in multiple sclerosis (MS). Mechanisms mediating the beneficial effects of DR include the regulation of pro- and anti-inflammatory signalling molecules and gut microbiome remodelling. This article summarises the preclinical evidence supporting the role of DR in attenuating disease in animal models of MS and the developing clinical evidence indicating the safety and feasibility of such DR interventions in people with MS (pwMS).

Multiple sclerosis (MS) is considered an autoimmune disease of the central nervous system (CNS), resulting from the complex interplay between genetic and environmental risk factors. Several epidemiological studies conducted over the last decade have established the association between early-life obesity and elevated future risk of MS development [1]. Overweight and obesity (BMI ≥25 or 30, respectively) in adolescents and young adults increased MS risk by two-fold [2-5]. Mendelian randomisation studies have correlated genetic determinants of high BMI with heightened MS susceptibility, accounting for possible confounding lifestyle and socioeconomic factors and supporting a causal relationship between obesity and MS [6-7]. Moreover, obesity was associated with an almost two-fold increased relapse risk, greater annual increase in disability [8], and higher brain volume loss [9].

Multiple mechanisms may underlie the obesity-mediated increase of MS risk, some of which are not clearly understood and are the subject of ongoing investigations. Firstly, obesity is characterised by chronic low-grade inflammation with increased secretion of inflammatory mediators including IL-6, IL-12 and TNF-α and enhanced production of reactive oxygen species by adipose tissue macrophages [10-11]. Furthermore, higher adiposity is associated with increased serum levels of leptin, a pro-inflammatory adipokine [12]. This chronic inflammatory state may act to predispose overweight and obese individuals to the development of autoimmunity. Moreover, obesity is linked to dysbiotic alterations of the gut microbiota [13-14]. The gut microbiota is emerging as a potential modulator of pathogenic immune responses, with animal studies providing evidence for the role of gut microbiota in regulating T lymphocyte differentiation, CNS inflammation and microglia function, as well as myelination and blood-brain barrier integrity [15-18]. Correspondingly, people with MS (pwMS) display moderate gut microbiota dysbiosis [19,20].

Dietary restriction (DR) without malnutrition is a powerful intervention shown to extend healthy lifespan in many animal species, including non-human primates [21]. Furthermore, DR promotes weight loss and reduces multiple markers of inflammation in humans and also the experimental autoimmune encephalomyelitis (EAE) model of MS [22-27]. DR also prevents demyelination and promotes remyelination in toxin-induced models of MS [26,28-30]. In this article, we will review the beneficial effects of DR, including its ability to lower levels of pro-inflammatory molecules and reshape gut microbiome composition, highlighting the potential utility of DR for protecting against neuroinflammation and demyelination in pwMS.

Dietary restriction

Dietary restriction (DR) is defined here as a reduction in total food intake, either chronically or intermittently, whilst maintaining proper nutrition. Chronic DR, also known as calorie restriction (CR), entails a variable reduction in energy intake every day (usually ~20% in humans and up to 40-50% in preclinical models), wherein meal frequency remains unchanged. Intermittent fasting (IF) involves complete abstinence or substantial reduction of energy intake for periods of time, usually

12 hours or longer, and unrestricted feeding during meal times [31]. Examples of IF regimens include time-restricted feeding (TRF), in which total daily food intake is limited to a specific timeframe within the day (typically lasting between 6-8 hours), fasting or drastic caloric reduction (e.g., consumption of 500 calories per day) on alternate days (alternate day fasting or alternate day modified fasting), fasting for 2 days per week (5:2 diet), and fasting mimicking diet (FMD) which comprises several days (usually 5-7 days in humans or 3 days in preclinical models) of drastically reduced calorie intake [32]. Collectively, DR interventions can induce healthy weight loss in overweight individuals and more importantly, exert beneficial anti-inflammatory and neuroprotective effects both in relation to and independent of reduced adiposity [24].

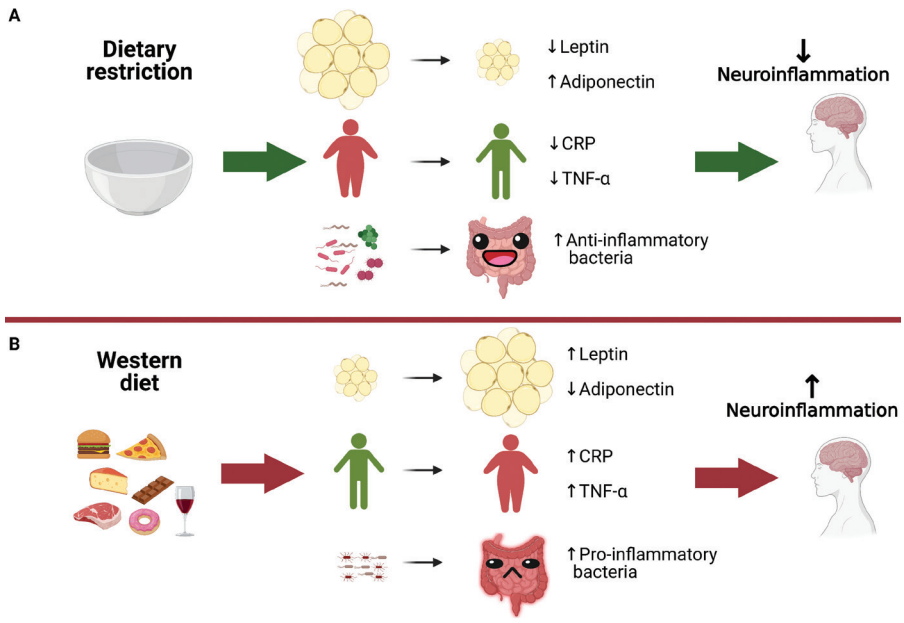


Figure 1. Main effects of DR compared to a Western diet regimen. A. Lowering caloric intake determines a reduction in adiposity, with a consequent decrease in leptin and increase in adiponectin, lower levels of systemic inflammation and a modulatory effect on the gut microbiome. B. On the contrary a Western diet (WD) regimen increases adiposity, the production of pro-inflammatory cytokines and adipokines and the abundance of pro-inflammatory gut bacteria. These diet-induced systemic changes will impact neuroinflammation.

Balancing the pro-inflammatory versus anti-inflammatory cytokine milieu

The adipose tissue serves as not only an energy reservoir, but also an endocrine organ, secreting cytokines and hormones, collectively termed "adipokines", which can modulate immune responses [33]. A standard Western diet (WD) is characterised by the regular intake of high amounts of processed foods, red meat, high-fat dairy products, high-sugar, and pre-packaged foods and leads to excess adiposity with consequent adipokine dysregulation characterised by upregulation of pro-inflammatory molecules, such as leptin, C-reactive protein, TNFα and IL-6, and down-regulation of anti-inflammatory factors, such as adiponectin [34] (Figure 1). CR and IF interventions reduce visceral adiposity in humans [35,36] and restore the balance between pro-inflammatory and anti-inflammatory mediators in animals and humans [22,37,38]. DR reliably decreases leptin levels and increases adiponectin levels in animals and humans [24,39,40] (Figure 1). Pertinently, pwMS display elevated leptin and reduced adiponectin levels, with leptin concentration correlating negatively with the number of regulatory T cells [41,42]. Hence, DR restriction may be an effective tool for tempering the dysregulated cytokine milieu in MS (Figure 1).

Gut microbiome and neuroinflammation

A considerable number of studies have reported alterations in the gut microbiome composition in pwMS. Unfortunately, there is little overlap in results between studies and only some taxa are consistently reported as differentially represented. Several studies reported an over-representation of the genera *Akkermansia* in pwMS compared to healthy controls [15,19,43] together with a reduced abundance of *Bacteroidaceae, Faecalibacterium, Clostridium* species and *Prevotella* strains [44-46]. Both *Clostridium* and *Bacteroidaceae* have immunomodulatory effects, promoting the differentiation of murine regulatory T cells and the production of IL-10 [47-49] (Figure 1). It is unclear whether these gut-microbiota alterations in MS are a consequence of the disease or contribute to disease pathogenesis. However, in support of a real pathogenic role is the finding that gut microbiota or gut-derived molecules obtained from pwMS can modulate disease in the main MS animal model, EAE, when transferred into mice [15,43]. Specifically, recipient mice inoculated with microbiota from pwMS showed increased incidence of spontaneous EAE [43] and exacerbated EAE clinical severity with decreased regulatory T cell expression compared to those inoculated with healthy control microbiota [15]. Furthermore, extracts from specific MS-associated bacterial species increased in vitro differentiation of pathogenic CD4+ T helper 1 cells, whilst extracts from bacterial species that were diminished in pwMS boosted regulatory T cell differentiation [15]. These findings indicate a role for MS-related microbiota in shaping immune phenotypes and function.

DR interventions have the potential to positively influence gut microbiota composition. For example, life-long calorie restriction changed gut microbiota structure in mice, as marked by an enrichment of anti-inflammatory bacterial strains including *Lactobacilli* [50]. Microbial alterations were accompanied by reductions in serum levels of lipopolysaccharide-binding protein, a marker of gut-derived endotoxin load [50], which is also correlated with systemic inflammation.

Search strategy

To find studies testing DR regimens in preclinical models of MS and pwMS, a literature search was conducted in PubMed in September 2021 using the search string ((multiple sclerosis) OR (CNS autoimmunity) OR (experimental autoimmune encephalomyelitis) OR (experimental allergic encephalomyelitis)) AND ((dietary restriction) OR (calorie restriction) OR (caloric restriction) OR (fasting) OR (intermittent)). After reading titles and abstracts, only original research articles investigating restriction of total food intake (not specific macronutrients or micronutrients) were included.

Effects of dietary restriction in preclinical models

There is strong preclinical evidence supporting the efficacy of DR regimens, including both CR and IF, in protecting against neuroinflammation and demyelination (Table 1). The preventative effects of CR in EAE were first demonstrated in 2004 [51]. Prior to immunisation, Lewis rats were subjected to 15 days of severe CR, equivalent to 66% reduction from ad libitum intake and then monitored for EAE symptoms. Whilst 8 out of 9 ad libitum-fed rats developed clinical signs of EAE, calorie-restricted rats did not display any disease manifestations and demonstrated reduced lymphocyte response to T-cell mitogen concanavalin A [51]. A follow-up study utilising the same 15-day CR protocol revealed that moderate CR (33% reduction) was insufficient for preventing EAE progression, whilst severe 66% CR-induced inhibition of EAE development was likely mediated by decreased IFN-γ production [52]. Our group demonstrated that a month of 40% CR in mice delayed EAE clinical onset and decreased disease severity [23]. CR was associated with increased levels of adiponectin and corticosterone, and decreased levels of IL-6 and leptin [23].

IF administered before immunisation and throughout the course of EAE similarly delayed disease onset and reduced the incidence and severity of disease [24,53]. Along with attenu-

Table 1. Summary of the studies that tested DR regimens in MS animal models

Type of DR	DR effects on inflammatory or other brain pathology markers	DR effects	Reference
66% CR for 15 days before EAE induction and throughout disease course	↓ lymphoid cell mitogenic response to concanavalin A	Prevents EAE	[51]
66% CR for 15 days before EAE induction and throughout disease course	Alters lymphocyte composition in lymphoid organs, ↓ IFN-γ production	Prevents EAE	[52]
40% CR for 5 weeks before EAE induction and throughout disease course	↑ corticosterone and adiponectin, ↓ leptin	Ameliorates EAE clinical course	[23]
IF – alternate-day fasting for 8 weeks before EAE induction and throughout disease course	Not reported	Ameliorates EAE clinical course and reduces incidence of disease	[53]
IF – alternate-day fasting for 4 weeks before EAE induction and throughout disease course	↓ Th17 cells, ↑ T regulatory cells in small intestine lamina propria	Ameliorates EAE clinical course and reduces incidence of disease	[24]
IF – alternate-day fasting for 4 weeks before EAE induction and throughout disease course	↓ monocyte infiltration in the spinal cord, ↓ monocyte expression of TNFα, IL-1β, CXCL2 and CXCL10	Ameliorates EAE clinical course and reduces incidence of disease	[25]
FMD – 3 cycles of very-low-calorie and low-protein diet for 3 days per week after EAE induction	↓ immune cell infiltration in the spinal cord, ↑ autoreactive lymphocyte apoptosis, ↑ oligodendrocyte differentiation	Ameliorates EAE clinical course and reduces incidence of disease	[26]
FMD – 2 cycles of 67% calorie reduction for 3 days per week after EAE induction	↓ immune cell infiltration in the spinal cord, ↑ oligodendrocyte precursor cells in the spinal cord, ↑ BDNF expression	Ameliorates EAE clinical course and reduces incidence of disease	[27]
33% CR for 4 weeks	↑ remyelination, ↑ mRNA expression of BDNF, ↓ astrogliosis and microgliosis, ↑ oligodendrogenesis	Ameliorates cuprizone-induced demyelination	[28]
CR via 10% cellulose diet for 6 weeks	↓ demyelination, ↓ M1 iNOS$^+$ macrophage/microglia, ↑ M2 arginase 1$^+$ macrophage/microglia, ↓ corpus callosum TNFα expression	Ameliorates cuprizone-induced demyelination	[29]
IF – alternate-day fasting for 6 months	↑ remyelination after induced focal demyelination, ↑ oligodendrocyte progenitor cell differentiation	Enhances remyelination in aged rats	[30]

Abbreviations: ↑, increase; ↓, decrease; BDNF, brain-derived neurotrophic factor; CR, calorie restriction; CXCL2, chemokine (C-X-C motif) ligand 2; CXCL10, chemokine (C-X-C motif) ligand 10; DR, dietary restriction; EAE, experimental autoimmune encephalomyelitis; FMD, fasting mimicking diet; IF, intermittent fasting; IFN-γ, interferon gamma; IL-1β, interleukin 1 beta; iNOS, inducible nitric oxide synthase; mRNA, messenger ribonucleic acid; Th17, T-helper 17; TNFα, tumour necrosis factor alpha.

ation of EAE, IF decreased Th17 cells and increased regulatory T cells in the small intestine lamina propria and also increased the diversity and altered the composition of the gut microbiome [24]. Notably, gut microbiota transfer from IF mice to naïve EAE recipients recapitulated the protective effects of IF, suggesting the role of microbiota in mediating the favorable effects of IF [24]. Another study found that IF conferred protection against EAE by preventing monocyte recruitment to the CNS and downregulating monocyte expression of pro-inflammatory genes including TNFα, IL-1β, CXCL2 and CXCL10 [25]. Importantly, IF did not compromise the immune response to bacterial infection or tissue injury [25]. FMD, a form of IF applied in cycles which consist of several days of severe reduction in calorie intake followed by ad libitum feeding, has also been effective in ameliorating EAE [26,27]. FMD administered therapeutically after disease onset suppressed autoimmunity as evidenced by reduced pro-inflammatory cytokines, Th1 and Th17 cells and antigen-presenting cells and promoted recovery as demonstrated by enhanced oligodendrocyte regeneration, remyelination [26], and brain-derived neurotrophic factor (BDNF) expression [27].

The beneficial effects of DR have also been reproduced in preclinical models of demyelination and remyelination [26,28-30]. In the cuprizone model (in which oligodendrocyte death is caused by administration of a toxin), 33% DR improved coordination and balance and enhanced corpus callosum remyelination. DR reduced astrogliosis and microgliosis and expanded the oligodendrocyte population [28]. Further, DR skewed macrophage/microglia polarisation towards the anti-inflammatory M2 phenotype in the cuprizone model [29]. Macrophage/microglia phenotypic switching may be modulated by activation of nutrient sensors and modulation of immunometabolic pathways [54,55]. In another study, 6 months of alternate-day fasting increased remyelination in aged rats after focal demyelination induced by ethidium bromide injection through restoring the regenerative capacity of oligodendrocyte precursors [30]. Overall, preclinical data provide promising evidence of the preventative and therapeutic effects of DR in dampening autoimmune and demyelinating responses in experimental models of MS.

Effects of dietary restriction in people with MS

The effects, safety and feasibility of DR in pwMS have been investigated in several studies (Table 2). A 6-month prospective study of 40 pwMS with mild disability (expanded disability status scale-EDSS score ≤3) found that Ramadan fasting, lasting approximately 13 hours daily for a month (however fasting periods can vary between 11 to 18 hours depending on year and geographical location), was safe and did not exacerbate disease [56]. Ramadan fasting (14-hour daily fast) in pwMS with mild disability also significantly boosted physical and mental health measures including energy, health perception and emotional well-being [57]. Several interventional DR regimens have been tested in pwMS. A single 7-day cycle of FMD followed by a Mediterranean diet for 6 months improved health-related quality of life metrics and mildly reduced EDSS scores [26]. We compared the effects of 15 days of IF (intake limited to 500 calories every second day) and regular feeding in 16 pwMS undergoing acute MS relapse and receiving corticosteroid treatment [24]. IF was well-tolerated, reduced leptin levels, and recapitulated gut microbiome

Table 2. Summary of studies that tested DR regimens in people with MS (pwMS)

Type of DR and duration	Study design, sample size, subject clinical characteristics	DR effects on inflammatory markers	Main outcomes of DR in pwMS	Reference
Ramadan fasting 13-hour daily fasting period for 1 month	Prospective study (subjects followed for 6 months after Ramadan to assess clinical outcomes) 2 groups – (1) pwMS who fasted during Ramadan, (2) pwMS who did not fast during Ramadan matched for age, gender, EDSS scores and relapse rates (n=40 per group) pwMS with mild disability (EDSS ≤3), type of MS not specified	Not reported	Well tolerated No significant differences in EDSS scores or number of clinical relapses between 2 groups	[56]
Ramadan fasting 14-hour daily fasting period for 1 month	Prospective study (subjects assessed before and after month of Ramadan) 1 group – pwMS who fasted during Ramadan (n=218) pwMS (RRMS) with mild disability (EDSS ≤3)	Not reported	Significantly improves physical health and mental health composites of QOL including role limitations due to emotional problems, emotional wellbeing, energy, health perception, sexual function	[57]
Single cycle of FMD for 7 days (200-350 kcal per day, consisting of vegetable broth/juice and linseed oil) followed by Mediterranean diet (MD) for 6 months	Single-centre, randomised controlled trial 3 dietary intervention groups – (1) 7 days FMD followed by MD for 6 months, (2) ketogenic diet for 6 months, and control diet for 6 months (n=20 per group) pwMS (RRMS) with EDSS ≤6.5	Slight ↓ blood lymphocyte and WBC counts after 6 months of FMD + MD compared to control diet (p=0.07) >20% reduction in lymphocyte count directly after 7 days of FMD in 72% of pwMS given FMD treatment	Well-tolerated (100% compliance rate), safe and feasible Significantly improves health-related QOL measures including overall QOL, change in health, physical health composite, and mental health composite compared to control; mild reduction in EDSS scores	[26]
IF – alternate-day fasting (fasting days restricted to 500 kcal) 15 days	Single-centre randomised controlled pilot trial 2 groups, both given same corticosteroid treatment for acute relapse – (1) pwMS subjected to IF, (2) control group of pwMS eating their regular diet (n=8 per group); no significant differences in age, BMI and EDSS score between groups pwMS (RRMS) experiencing acute clinical relapse at time of study; BMI ≥23	↓ leptin ↓ blood B cell and naïve $CD4^+$ count ↑ Treg cell in vitro suppressive capacity	Well tolerated, safe and feasible, ↓ BMI at day 15	[24]
22% CR or IF (75% calorie reduction for 2 days per week) 8 weeks, with all meals delivered to homes	Single-centre randomised controlled trial 3 groups – (1) pwMS subjected to CR, (2) pwMS subjected to IF, (3) control group pwMS subjected to diet comprising 100% of calorie needs (n=12 per group) pwMS (RRMS) with EDSS <6 and new lesion or relapse within the past 2 years; BMI ≥23	Not reported	Safe and feasible Both 22% CR and IF induce weight loss, improve emotional wellbeing, and have no negative impact on fatigue or sleep quality; ↓ adherence to diet in IF group compared to CR group (measured as per-day difference in calorie consumption from assigned intake)	[58]
22% CR or IF (75% calorie reduction for 2 days per week) 48 weeks (meals delivered in first 8 weeks, followed by self-directed IF (75% calorie reduction for 2 days per week) in last 40 weeks)	Single-centre randomised controlled trial 3 groups in first 8 weeks– (1) pwMS subjected to CR, (2) pwMS subjected to IF, (3) control group pwMS subjected diet comprising 100% of calorie needs (n=12 per group); followed by transition to IF for all groups pwMS (RRMS) with EDSS <6 and new lesion or relapse within the past 2 years; BMI ≥23	Not reported	Safe and feasible, but poor adherence (only 16% of remaining participants reporting adherence to IF at 48 weeks) No significant differences in weight or patient-reported outcomes (fatigue, sleep quality, quality of life)	[59]
22% CR or IF (75% calorie reduction for 2 days per week) 6 months	Single-centre randomised controlled trial Participants allowed to select either (1) CR (n=11) or (2) IF (n=8); 5 CR and 5 IF participants randomised to receive weekly text message communication pwMS (RRMS) receiving natalizumab with BMI ≥25	Not reported	Safe and feasible with 50% adherence Text message communication did not improve adherence or patient-reported outcomes (fatigue, sleep quality, quality of life)	[59]
TRF (16-hour daily fasting period) 6 months	Single-centre randomised controlled trial 2 groups – (1) pwMS undergoing TRF, (2) control group of pwMS eating their regular diet (n=12 per group) pwMS (RRMS) receiving natalizumab	Not reported	Safe and feasible, with 83.3% adherence No significant differences in weight or patient-reported outcomes (fatigue, sleep quality, quality of life)	[59]

Abbreviations: ↑, increase; ↓, decrease; BMI, body mass index; CR, calorie restriction; DR, dietary restriction; EDSS, expanded disability status scale; FMD, fasting mimicking diet; IF, intermittent fasting; pwMS, people with MS; QOL, quality of life; RRMS, relapsing-remitting multiple sclerosis; Treg, regulatory T cell; TRF, time restricted feeding; WBC, white blood cell.

alterations seen in EAE mice subjected to IF [24]. An 8-week randomised controlled study assessed the effects of 22% CR and IF (2 days of 75% reduction in energy intake and 5 days of ad libitum feeding) in 36 pwMS [58]. Both dietary regimens were concluded to be safe and feasible and were associated with significant improvements in emotional health, whilst adherence was greater in the CR regimen [58]. The same research group performed 6-month pragmatic randomised controlled trials of 22% CR, IF (75% calorie reduction for 2 days per week) and TRF (in which consumption of all daily calories was limited to an 8-hour interval), with feasibility and patient adherence as primary outcome measures [59]. Whilst all DR regimens tested proved to be feasible, self-reported adherence was much higher for the TRF diet than both CR and IF regimens over 6 months, which both demonstrated poor long-term adherence [59]. Altogether, a variety of different DR interventions have proven to be safe and feasible in pwMS.

Presently, there are several ongoing clinical trials of DR in pwMS. To investigate whether the anti-inflammatory and gut microbiome-modulating properties of IF observed in preclinical studies are recapitulated in pwMS, we are currently conducting a 12-week randomised controlled study investigating the effects of IF (2 fasting days/week) on peripheral blood immunological parameters, metabolic profiles and gut microbiota composition in pwMS (NCT03539094). Other ongoing trials are focused on determining whether DR can improve clinical outcomes, which is currently inconclusive. An 18-month, 3-armed study is comparing the occurrence of new cerebral lesions as measured by magnetic resonance imaging between 111 pwMS randomly assigned either a ketogenic diet, an IF regimen consisting of TRF (fasting for 14 hours per day) and an additional 1 week of fasting every 6 months, or a control vegetarian-based diet (NCT03508414). Lastly, a study is investigating the effects of 15-20% calorie restriction, with or without abstinence from dairy and gluten products, on MS progression as well as immune cell activity and metabolism (NCT04042415).

Potential risks of DR

Whilst no serious adverse effects have been reported in clinical trials of DR in pwMS, it is important to be aware of the potential risks that may accompany DR and potential contraindications that may render individuals unsuitable for DR. Mild symptoms experienced by pwMS undergoing DR included fatigue and headaches [26,58,59], although these may or may not be directly related to DR. An assessment of adverse events occurring during medically supervised water-only fasting for ≥2 days consecutively, with a patient cohort not specific to pwMS, described fatigue, insomnia, nausea, headache, hypertension (which was likely incidental due to pre-existing hypertension), presyncope, dyspepsia, and back pain as effects present in more than 25% of visits (from a total of 768 visits), in order of frequency [60]. Contraindications to DR may include low body weight or BMI, pregnancy, very young or old age, comorbidities such as diabetes, and prescription of specific medications. Further, clinical trials have been conducted only in relapsing-remitting MS (RRMS) patients with mild to moderate disability, thus DR may not be appropriate for pwMS with severe disability.

Conclusion and future perspectives

Since the characterisation of obesity as a risk factor for MS, subsequent investigations into the mechanisms underlying this association have implicated the involvement of cytokines from adipose tissue and dysbiotic microbiota in MS. In particular, DR has emerged as an effective method of counteracting the detrimental effects associated with increased adiposity. Indeed, mounting preclinical evidence suggests that DR exerts neuroprotective effects, which are mediated by the modulation of pro- and anti-inflammatory molecules and alterations to the gut microbiome, among other possible mechanisms. Clinical trials have confirmed the safety and feasibility of various DR regimens and demonstrated DR-induced improvements in quality of life measures in pwMS. There is a need for larger and longer randomised controlled studies to produce strong definitive evidence linking DR with improved clinical outcomes, before any clinical recommendations can be made. Long-term patient adherence has been a barrier to determining whether DR can improve clinical disease outcomes and is an important factor to consider when selecting any particular DR regimen. It's important to recognise that DR alone might not be effective in significantly improving clinical outcomes. However, it can be considered a valuable complementary intervention to commonly used disease modifying treatments and future trials should take into consideration the possibility of an integrated approach. Additionally, the potential risks of DR need to be understood and vulnerable populations of pwMS unsuited to DR regimens need to be identified.

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HOW DOES FINTEPLA▼ (FENFLURAMINE) SET A NEW STANDARD IN SEIZURE CONTROL FOR PEOPLE WITH DRAVET SYNDROME?

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[1]

Dravet syndrome is a rare form of epilepsy with many unmet needs[2]

Seizures start in infancy and are typically severe and resistant to treatment[3,4]

Many patients take ≥3 AEDs, yet continue to experience ≥4 seizures per month[4,5]

People with Dravet syndrome have an increased risk of premature mortality (12%–21%)[6,7]

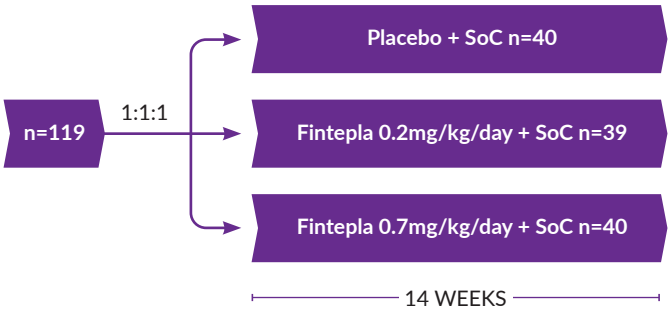
~50% of all deaths in children and young adults with Dravet syndrome are due to SUDEP[7]

Increasing the number of seizure-free days significantly improves patient QoL[8]

Fintepla has been assessed in Phase 3 clinical trials. Here are some key findings:

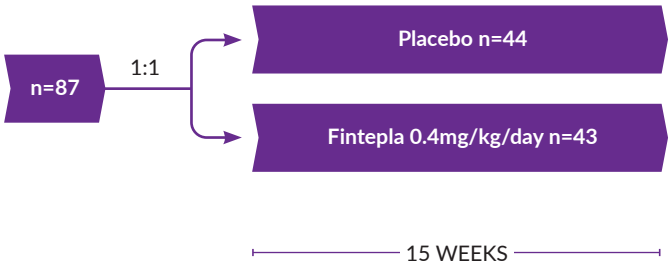
Study 1[9]

A randomised, double-blind, placebo-controlled clinical trial to assess the safety and efficacy of adjunctive Fintepla in Dravet syndrome



Study 2[10]

A randomised, double-blind, placebo-controlled clinical trial of Fintepla as part of a stiripentol-inclusive AED regimen in Dravet syndrome



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

Fintepla provided a profound reduction in convulsive seizure frequency and prolonged periods of seizure freedom in both studies.

	Study 1[9] (Fintepla 0.7mg/kg/day + SoC)	Study 2[10] (Fintepla 0.4mg/kg/day + stiripentol)
Relative reduction in mean monthly convulsive seizure frequency with Fintepla vs placebo (primary endpoint)	**62.3%** greater than placebo (*P*<0.0001)	**54.0%** greater than placebo (*P*<0.001)
Reduction in the median monthly convulsive seizure frequency from baseline (secondary endpoint)	**74.9%** (vs 19.2% with placebo; *P*<0.0001)	**63.1%** (vs 1.1% with placebo; *P*<0.001)
Median longest seizure-free interval (key secondary endpoint)	**25 days** (vs 9.5 with placebo; *P*<0.0001)	**22 days** (vs 13 with placebo; *P*=0.004)
Rate of near seizure freedom* (endpoint of interest)	**25%** (vs 0% with placebo)**	**12%** (vs 0% with placebo; *P*=0.03)

Fintepla significantly reduces day-to-day seizure burden in Dravet syndrome, which may help reduce the physical and emotional toll of the disease and improve health-related QoL for both patients and their caregivers.[9,10]

Fintepla is generally well-tolerated:

- The most commonly reported AEs are decreased appetite (44.2%), diarrhoea (30.8%), pyrexia (25.6%), fatigue (25.6%), upper respiratory tract infection (20.5%), lethargy (17.5%), somnolence (15.4%) and bronchitis (11.6%)[8]
- There have been no cases of valvulopathy or pulmonary hypertension[9–12]

*Near seizure freedom defined as ≤1 convulsive seizures during the treatment period. **Statistical significance not reported.
AED, antiepileptic drug; QoL, quality of life; SoC, standard of care; SUDEP, sudden unexpected death in epilepsy.

Consider Fintepla as your first line add-on option (when changing therapy) either in place of stiripentol or after stiripentol

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**.

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 60 mL = £901.44, 120 mL = £1802.88 and 360 mL = £5408.65
Job Code: UK- FIN1-2100051 **Date of Preparation:** August 2021

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Zogenix International Limited on 0800 060 8767 or email medinfo.eu@zogenix.com.

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Keeping people with aphasia worldwide "COVID-informed" amid and after the pandemic

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Abstract
Aphasia is an acquired language disorder commonly caused by a stroke or brain injury. A slowly growing number of studies have emerged reporting the psychosocial disruptions experienced by people with aphasia (PWA) in the present COVID-19 pandemic. To extend this topic of better addressing PWA's rehabilitation needs, this paper aims to draw attention to the significance of helping PWA stay "COVID-informed" through the use of resources that are communicatively-accessible. Keeping PWA abreast of the evolution of the pandemic can reasonably ensure they stay connected to their society, even without an actual physical presence in their community. However, aphasia-friendly health information is currently available predominantly in English only. Similar materials are relatively scarce in other languages and not necessarily updated, albeit such a need for these resources is apparent globally. It is essential that healthcare providers ensure that accessible, comprehensible, high-quality and reliable health-related resources are made available for PWA; this will ultimately benefit them to navigate the pandemic and prepare for the post-COVID era.

Keywords: aphasia, COVID-19, aphasia-friendly, accessible information, health literacy

Aphasia is an acquired language disorder commonly caused by a left-hemispheric stroke or an injury to brain regions responsible for language [1]. It can impair one's auditory comprehension, verbal expression, reading, and/or writing across different performance levels such as processing of words, phrases, sentences, and narrative discourse [2]. At present, approximately one in 270 people in the UK (0.37% of the population) [3] and about one in 250 people in the US (0.40% of the population) are living with aphasia [4].

A recent article by Ellis and Jacobs [5] has summarised the reduction in psychological well-being among people with aphasia (PWA) due to social isolation amid COVID-19, and justified the fundamental needs to promote "physical distancing and social connectedness" aphasia treatment and support groups that can benefit PWA's social and emotional fulfilment. This echoed not only the reported communication challenges and social inactivity experienced by PWA during lockdowns [6], but also the exacerbating side effects such as stress and depression in PWA as the pandemic progressed [7]. To extend this topic of better addressing PWA's rehabilitation needs, this article aims to draw attention to the significance of helping PWA stay informed about the pandemic.

Health literacy refers to the degree to which one can identify, understand, and use information and services to inform health-related decisions and actions [8]. Clinically, it is important that healthcare service receivers, including PWA and their carers, can easily obtain health information related to COVID-19. This is particularly the case given that the evolving situation of this pandemic is multifaceted in nature and, therefore, complicated. According to a recent investigation conducted to compare readability of existing official public health information on COVID-19 written by three international public health agencies and governments of 15 countries [9], these materials available on the internet are far too complex for the general public to understand, with a reading level of approximately three grades higher than the recommended "eighth-grade" level suggested by The American Medical Association, National Institutes of Health, and Centers for Disease Control and Prevention (CDC) [10]. A similar cross-sectional study based on 61 online educational articles about COVID-19 [11] paralleled the above findings. Specifically, these articles contained information that was too difficult for the general population to read as all of them failed to meet the recommended "fifth- to sixth-grade" level (i.e., all exceeded the reading level of an 11-12 year old reader) suggested by United States Department of Health and Human Services. As further stated by The Center for Literacy & Disability Studies at University of North Carolina at Chapel Hill [12], although many written resources

about COVID-19 have been created for the general public, these materials were generally found to be too demanding and complicated for those with an intellectual and/or developmental disability (who typically demonstrate a "third-grade" written or auditory comprehension level, or lower competency). This finding was surprising because it implied that even for the language-unimpaired audience or readers, keeping up with updated and accurate knowledge about the pandemic (such as its origin and cause(s), spreading mechanism and related symptoms, diagnosis, safety measures, and key rehabilitation principles including vaccination options and side effects) can be a daunting and difficult task. In fact, an article published in early 2021 that reviewed and compiled studies on appropriate reading level of COVID-19 online information [13] suggested that this problem still persists and has not improved – the readability level of most, if not all, existing COVID-19 education/information resources is far exceeding that recommended for patient information. More critically, if solely relying on these existing written (educational) materials, the PWA audience will arguably face more challenges in understanding the characteristics of COVID-19 and keeping abreast of the evolution and latest information on the coronavirus because of their underlying difficulties in processing language materials and inherent selective cognitive problems [7,14].

Amid the pandemic, it is crucial that PWA are provided with updated information and/or resources about COVID-19 that are communicatively-accessible, i.e., aphasia-friendly [15]. Specifically, the format and typography of these materials should ensure readability in the PWA population, through (a) careful control of text complexity and writing style (e.g., use of short and simple sentences, use of straightforward language, avoiding technical terminology or complex syntax, etc.) (b) considerations of formatting and design (e.g., increased print size, use of symbols, bullet points, ample spacing, headings and/or signposting, bolding key words, etc.), and (c) inclusion of appropriate images or graphics (e.g., photographs or pictures that directly support the text). Currently, such materials that fulfil the above-mentioned aphasia-friendly criteria are available predominantly in English only (e.g., focusing mainly on explanations of some major and basic COVID facts [16,17]), but the content of these resources may not necessarily be updated. Comparable materials are also arguably scarce in other languages, albeit the need for these related materials is apparent globally. In April 2020, the CDC [18] made some up-to-date COVID-19 materials available in an easy-to-read format. The content, primarily developed for those who read or listen with understanding below a third-grade level, generally follows many aphasia-friendly principles such as having simple sentence structure, additional white space, and a clear and simple font. Multiple topics are addressed as separate pages/links that are available for download and/or printing. Practitioners who work with PWA may refer to this type of platform, or similar sites in the National Health Service (NHS) (e.g., https://www.nhs.uk/conditions/coronavirus-covid-19/) or Public Health England (e.g., https://www.gov.uk/coronavirus), to share updated information about the pandemic. In addition, some UK-based nonprofit organisations (e.g., Social Care Institute for Excellence, SCIE; https://www.scie.org.uk/care-providers/coronavirus-covid-19) have also translated more accessible information on COVID-19 that may be appropriate for PWA. Finally, the presentation of the materials on the internet will mean that PWA can have the content read to them by one of several easily accessed screen readers (such as text-to-speech systems) to further facilitate comprehension.

The earlier Delta variant of coronavirus and the most recent Omicron mutations are of global concern. There has been disparity between the availability of accessible information on COVID-19 vaccination and the need to better understand health information among the general population [19]. This is worrying because it puts individuals at risk from COVID-19 and allows more rapid spread of infection in the community. In Autumn 2020, the CDC published guidelines to instruct all state health departments to develop inclusive vaccine communication strategies guided by the Americans with Disabilities Act (ADA) and Plain Language Act [20]. Currently, some additional and updated resources are also available to help PWA navigate the vaccine scheduling process (e.g., https://www.marchofdimes.ca/en-ca/aboutus/newsroom/cia/Pages/Covid19-aphasia-resources.aspx). It is believed that good use of the above-mentioned materials by the PWA (and caregivers) as well as timely awareness among service receivers facilitated by clinicians can reasonably minimise the spread of vaccine misinformation within the aphasia community.

To a certain extent, helping PWA stay up-to-date on (or become adequately informed about) the ever-changing pandemic is a way to facilitate their staying connected to their society, even without a physical presence in the community. The need for aphasia-friendly health information is apparent worldwide, but very few studies at present have fully explored the potential disparate effects of the lack of resources in this needed format that can benefit non-English speaking PWA. Note that some general work on language equity for public health communication has already emphasised the disparity in availability of multilingual resources pertaining to medical and COVID-19 public health information [21]. In the UK, for example, although online COVID-19 information in English is readily available to the British public, corresponding translated versions targeting minority ethnicities and graphics-based materials are very limited [22], which could amplify the level of misunderstanding about the COVID-19 pandemic. More importantly, such a lack of these non-anglophone resources would further hinder the development of the more aphasia-friendly versions for communities of PWA with different language backgrounds.

Based on the perspective of PWA and their family members, Wallace and colleagues [23] examined and identified important aphasia treatment outcomes with reference to the International Classification of Functioning, Disability and Health (ICF) put forth by the World Health Organization. Apart from outcomes related to the ICF components of 'Activity/Participation' and 'Body functions', PWA also expressed a desire for (a) improved independence with daily routines and activities and (b) better health services and access to related information. In the current COVID context, this latter expectation becomes particularly relevant for PWA worldwide to stay motivated and lead a life successfully with aphasia [24,25], and can be easily achievable by ensuring information about the pandemic is accessible. Furthermore, the significant others of PWA can also be empowered through the use of aphasia-friendly resources to educate, support, and help their loved ones cope during the pandemic. Hence, it is essential that healthcare providers ensure that accessible, comprehensible, high-quality, and reliable health-related resources are made available for PWA, as part of an effort to keep them "COVID-informed". This will ultimately benefit PWA in terms of their better ability to navigate the pandemic and, in the near foreseeable future, prepare for the post-COVID era.

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Making information accessible for people with aphasia in healthcare

Abstract

People with aphasia are often unable to access healthcare due to difficulties understanding and using spoken and written language, which impacts every step of their healthcare journey and outcomes. This article argues that it is important to apply the principles of the NHS England Accessible Information Standards (2017) to people with aphasia so they can meet their health information needs and rights. The processes to enable people with aphasia to access and participate in spoken and written communication in healthcare and the methods for training and supporting healthcare staff need to be considered at an individual, service, and organisational level.

The accessible information standards (2017) state the need for organisations to ensure that individuals receive information in an accessible format and any communication support they need [1]. Whilst the accessible information standards relate primarily to people with sensory impairments and learning disabilities, this paper will outline the rationale, methods, and strategies for applying similar principles for people with aphasia.

Successful communication between healthcare professionals and patients is essential for engaging patients in their healthcare and improving outcomes [2]. Spoken communication is the medium through which information is exchanged and decisions made between healthcare professionals and their patients [2]. Written information is used to supplement education and support informed decision making [3]. People with aphasia have the same health information needs and rights as everyone else, however due to their language impairments, they are likely to struggle to understand spoken and written information [2,3]. Ineffective communication with people with aphasia can lead to frustration, exclusion from healthcare services and decision making, higher rates of medical errors and patient dissatisfaction [2,3,4]. This is further impacted by the limited knowledge, skills, and attitude of the healthcare professional [2,5].

Healthcare professionals acknowledge the challenges in communicating with people with aphasia. Communication impairments impede all healthcare activities including assessment, diagnosis, care, education, and therapy [6]. However, healthcare professionals often do not receive formal training in how to communicate with people with aphasia [2].

Consequently, written information needs to be adapted to enable people with aphasia to read with understanding [7]. Healthcare professionals should receive communication partner training interventions to enable participation of people with aphasia in their healthcare [2,8].

Making written information accessible

The aphasia literature highlights the benefits of making written information 'aphasia friendly'. It improves the ability to read and understand written information [3,7]. It increases knowledge and improves confidence [3]. Perhaps most importantly, it is preferred by people with aphasia [9]. However, it is acknowledged that there is no definition of 'aphasia friendly'.

A number of studies have set out to determine the criteria for aphasia friendly written material. There appears to be good consensus on the most beneficial adaptations of language, font, and formatting. Most studies agree on the need for 'simple language', large and sans serif fonts, highlighting key words in bold, minimising volume of text, and spacing out information [7,9,10,11]. However, the use of images and the length of adapted written material have proved more controversial. Some studies report no significant benefit of supporting written information with pictures [7]. The preference of people with aphasia varies [3]. However, the potential advantages of images are multiple and include: helping reading comprehension, adding interest, adding enjoyment, and aiding memory [9]. Consequently, most studies recommend the use of pictures unless considered unhelpful

Table 1 summarises the criteria recommended in the literature for making written information accessible.

Domain	Criteria
Language	Words and sentences that are short in length [9,11]

	Simplified vocab and syntax [7,9,11]
	Specifically, this means [11]:
	• Write sentences that express one idea
	• Use everyday words
	• Be careful in use of pronouns
	• Use canonical syntactic forms, which are:
	  • Simple sentences
	  • Sentences without connectives to join sentences such as 'and, or, but'
	  • Sentences that do not include embedded clauses
	  • Active voice (not passive)

	Numbers expressed as figures not words [10]
	Relevant content only [9]
Font	Large print, specifically size 14 or 16 [7,9,10,11]
	San serif fonts [9,10,11]
	Black text [9]
	Key information highlighted in bold [9,11]
Format	Not too much text [9]
	White space/spaced out information [7,9,10]
	Distinctive headings that are linked to content [9]
Use of images	Symbols considered least helpful [10]
	1-2 images per sentence [11]
	Put the picture under the sentence [11]
	Image must relate directly to key word [11]
	Image should convey the meaning of the sentence [11]
	Image must not be ambiguous [11]
	Image should not have extraneous details [11]
	Image should not be abstract or metaphorical [11]

Table 2: Possible supported communication strategies

Acknowledge competence	
Appropriate tone of voice	
Use of humour	
Acknowledge contributions	
Reveal competence	
Ensure comprehension	**Support expression**
Write down key words	Ask yes/no questions
Use gestures or pointing	Provide verbal and written options
Draw key concepts or use relevant pictures	Encourage writing, gesture, or drawing
Refer to material that makes the topic clear	Give the person with aphasia time
Summarise and verify the conversation	

by the person with aphasia [9,10]. Length is similarly contentious. Making written information aphasia friendly tends to increase the length of the material. This is a source of complaint for some people with aphasia [3] and is considered by some to place increased demand on working memory [7]. However, it is preferred by others provided the information is formatted appropriately [10].

Communication partner training

Communication partner training is an environmental intervention that trains individuals to use strategies and communication resources in their interactions with people with aphasia [12,13,14], and possibly the person with aphasia themselves [13]. The main aim is to increase the knowledge and communication skills of those trained and to improve the participation of people with

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aphasia in social or healthcare conversations [13]. It has been shown to yield positive outcomes for a range of aphasia severity levels and a range of communication partners, including healthcare staff [12,13].

Communication partner training can be person-specific or generic [12]. Generic communication partner training can be used to teach healthcare staff to use supportive techniques and materials that are applicable across people with aphasia in healthcare contexts [12]. Clinicians who receive communication partner training report increased knowledge, confidence, and skills in communicating with people with aphasia [2,5,13]. Furthermore, training can lead to service-level change for the benefit of people with aphasia [5]. However, there is some suggestion that training alone is not sufficient [5,6]. Opportunity for follow-up support or coaching sessions, practice in clinically relevant situations, and making relevant resources accessible appear to drive greater implementation success in combination with favourable organisational conditions [5,14]. Organisational change and support are key given that lack of leadership, time, workplace culture, and workload pressures pose the greatest barriers to implementation of communication partner training [5,6,14].

Consequently, when healthcare professionals are asked to describe their needs for communicating with people with aphasia, they ask for [8]:

- Increased knowledge of aphasia
- Increased skills in engaging with people with aphasia and training to use communication techniques and tools
- Organisational change such as provision of more time and adapting resources so they are aphasia friendly
- Changing the role of Speech & Language Therapists to provide training, act as role models, provide in-situ coaching, and make communication tools that are accessible to all healthcare professionals.

The role of SLTs in providing training, advocating for people with aphasia, and providing ongoing support is highlighted elsewhere in the literature [2,15].

Many communication partner training programmes have their origin in 'Supported Conversations for Adults with Aphasia' (SCA), which provides the communication partners with the methods and materials needed to support conversations with people with aphasia [15]. SCA advocates for communication partners acting as a resource for people with aphasia and to actively share responsibility for communication success [15]. Table 2 outlines some possible supported communication strategies from SCA [15].

Conclusion

In conclusion, making information accessible for people with aphasia in healthcare needs to be a key priority at an organisational level. The above overview of the literature has identified that due to inaccessibility of information, people with aphasia are not having their healthcare needs and rights met; this is impacting all their healthcare activities and outcomes. The literature also acknowledges the challenges faced by healthcare workers when giving spoken and written information to people with aphasia. To address this, the role of Speech and Language Therapists should evolve to encompass provision of training and support to healthcare workers to meet these needs. This will ensure that people with aphasia are able to access healthcare information equitably alongside everyone else.

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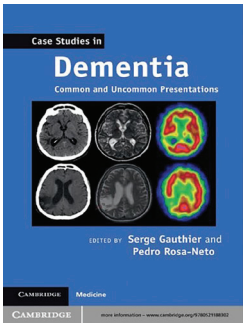
Case Studies in Dementia. Common and Uncommon Presentations

Case histories as a method of teaching have a long and venerable history since, despite their anecdotal and non-systematic nature, they are the idiom of clinical practice. This volume presents 34 cases seen by clinicians with an interest in disorders of cognitive function and is the successor volume to a collection of the same title with the same two editors published 10 years ago (Cambridge University Press, 2011).

Each case consists of 3 to 8 pages semi-structured as Case History, Past Medical History, Family History, Clinical Examination, Investigations, Discussion, and Take-Home Message(s), with appropriate illustrations of neuroimaging and, where available, neuropathology. The cases veer to the unusual, rather than the more typical fare of the cognitive clinic (no functional disorders here!), with rather more genetically determined cases than might be anticipated from experience in daily practice. The usual suspects are also here, including Alzheimer's disease, the clinically and genetically heterogeneous forms of the frontotemporal dementias, Lewy body dementia, vascular dementia, and prion disease. An Appendix draws together the diagnostic criteria for many of these disorders.

The book is well presented, like its predecessor, and will hopefully be of help both to those starting out in cognitive neurology and for more experienced clinicians wanting a refresher. That said, the reference lists contain nothing published more recently than 2018. A case of posterior cortical atrophy doesn't even allude to the diagnostic criteria of 2017, although they are included in the Appendix. So what happened in the interim prior to publication in 2021? Apparently not any type of copy editing by authors or editors, or how else to explain the pervasive errors. Some selected typos: "c09orf75" (Pxiii); "MRI FAIR imaging" (P19); "cerebral amyloid antipathy (CAA)" (sic! P23); "commodities" for comorbidities (P27); "persevere" for perseverate (P92); "Olczewski" for Olszewski (P93); "nycturia" for nocturia (P101); "free-radial damage" for free radical damage (P107); "cortical sensory myoclonus" for cortical sensory deficit (P155). There are also simple arithmetical errors in addition of cognitive test scores (P1 and 26), misnumbering of references (Case 4), and a whole paragraph describing neuroimaging has apparently been omitted in Case 15 (P70). Other issues troubled me: Is there a "unique gait disturbance" in iNPH (P128)? It would presumably be easier to diagnose if this were so. I'm still trying to get my head around reference to "*in vivo* post mortem validation studies" (P28; should this read "*in vivo* and post mortem validation studies"?), and what is one to make of "in a memory clinic, 12% of individuals with dementia were younger than 65. Among them, the most frequent diagnostic was MCI followed by AD and FTD." (P147). One expects better, particularly in a purportedly didactic text.



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Cognition services in MS: Where next?

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Objective

ACNR brought together an expert panel to review the current issues relating to the management of cognitive function in people living with multiple sclerosis, and the impact this has on their quality of life.

Expert Panel

Chair: Dawn Langdon, Professor of Neuropsychology
Khaled Abdel-Aziz, Consultant Neurologist
Noreen Barker, MS Nurse
Nathalie Fricker, person with MS
Susan Hourihan, Occupational Therapist
Nassif Mansour, General Practitioner with interest in MS
Claire Winchester Head of Information and Engagement, MS Trust
Carolyn Young, Consultant Neurologist

Medical writing by Synthesis Medical Ltd

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Introduction

DAWN LANGDON

Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disease of the central nervous system associated with a range of physical and mental symptoms [1]. Cognition is one of the "invisible symptoms" of MS [2]. Although it clearly has a significant impact on the lives of people with MS, it is not well understood or quantified in clinical practice [3].

In people with MS, the aspects of cognition most likely to be affected are memory, information processing speed, and problem solving. Problems in these areas may not be apparent to friends and family, or even to healthcare professionals. Yet many aspects of life are adversely affected by cognitive dysfunction, including employment, relationships, daily activities, physical independence and disease management. In fact, we know that employment is greatly affected for people with MS, even at very low levels of physical disability [4], and cognition is a significant part of this. There are also key safety issues related to cognition, such as driving ability or the risk of falls.

Importantly, cognition can also influence a person's disease management, leading to complications in medical decisions, rehabilitation benefit, and their coping skills [5]. The range of therapies available for MS have complex benefit-risk profiles, and engagement in informed consent and credible shared decision making is difficult for people with cognitive impairment. People who understand their medications are more likely to comply with their treatment schedule [6]. Cognition is not closely related to other disease variables, including MRI and so traditional medical investigations are not good indicators of an individual's cognitive status [7]. Self-reported cognition is a helpful way to understand patients' experience, but this is confounded by a number of psychosocial factors such as mood [8]. In order to fully understand cognition and measure the impact of therapy, a more objective measure is needed. For example, BICAMS (the Brief International Cognitive Assessment for Multiple Sclerosis) is a tool that can be administered in 15 minutes by most health professionals, and requires no specialist training [9].

There are a range of options for management of MS cognitive problems. Information for patients is a keystone [10]. Part of this is to support patients' understanding that positive lifestyle choices can slow the progress of the disease, including cognitive impairments, the "Brain Health" agenda [11]. Besides information and support, MS clinics can protect cognition by ensuring optimal MS treatment more broadly, including early intervention [12], disease modifying therapies [13] and management of co-morbidities [14]. Cognitive rehabilitation is a promising approach to treat cognitive dysfunction in MS, gaining empirical support over the last 10 years [15]. For example, cognitive rehabilitation can induce improvements in memory function and quality of life [16]. People with MS can participate successfully in self-directed, cognitive retraining on computer, which is less expensive to provide [17].

There is widespread support for the inclusion of cognitive assessment and management in routine clinical practice, but there are significant challenges [18]. An essential factor for implementation of the pathway is allocation of time during clinic appointments and within staff workloads [19]. Unfortunately, in the short term this model is not a viable framework for the NHS, and there remains a need for a more workable solution for people with MS. The recent COVID pandemic has interrupted clinical and research activity relating to MS cognition, however restoration of services and investigations is underway [20].

This panel was set up to review the current issues relating to the management of cognitive function in people living with MS, and the impact this has on their quality of life. The group met in March 2021 to share information about clinical challenges, and ideas for overcoming barriers.

Clinical challenges – what does the neurologist need in the clinic?

KHALED ABDEL-AZIZ

In current practice, cognitive testing is done at the individual neurologist's discretion. A more efficient approach to detect cognitive symptoms in people with MS would be to standardise routine cognitive assessments for all patients. But there are challenges to delivering cognitive assessments, both in specialist MS clinics and general neurology services. When considering what is needed to enable cognitive assessments to be included in standard care, it is important to recognise that MS clinics already cover a vast range of items, and there are time pressures. Consultant neurology follow-up appointments are typically 10-20 minutes, and cover relapses and symptom changes, scans, compliance, safety and side effects, as well as a physical examination and discussion of any new management options. However, there is value in including cognition as standard. Cognitive impairment is reported in 40-70% of people with MS and there is evidence that early cognitive impairment can predict clinical course [21,22]. Screening assists timely detection of cognitive deficits, thereby allowing patients to be referred for support at an earlier stage.

The current recommendation is that cognitive symptoms in MS should be screened annually [23,24], but this is difficult in practice. Gold-standard assessments such as MACFIMS (Minimal Assessment of Cognitive Function in MS) are time-consuming – taking up to 90 minutes with a neuropsychologist; measures such as Rao's take 30 minutes to administer, but at the expense of sensitivity. For an average clinic (~10 patients), this would require an additional capacity of 5-15 hours. There is an additional need to look alongside for confounding secondary factors such as depression or sleep problems. More practical options use shorter screening tools that can be delivered by any member of the healthcare team: BICAMS takes only 15 minutes, with comparable sensitivity to MACFIMs, or the SDMT (Symbol Digit Modalities Test) only five minutes. A quiet environment is also needed for cognitive screening to minimise distractions during timed assessments, but the reality of an NHS clinic is that it can be noisy, and there are constant interruptions. Patients may also bring partners or children with them.

Computer-based, self-administered tests may solve time issues [25,26,27], but a consensus is needed on how these can be used. Potential

advantages in addition to time savings in clinic include reduced inter-rater variability; drawbacks are uncontrolled test environments, and exclusion of patients without tablets or smart phones. In the future, perhaps hospital-based test centres run by a small number of staff could assess patients en masse. This would create a controlled environment, and could be combined with self-administered screening for depression, anxiety and fatigue. Although this would require initial investment, there would be long-term cost-savings in clinic and staff time.

Practical issues and daily management – what does the MS nurse see?

NOREEN BARKER

The role of the MS Specialist Nurse in the care of people with MS has changed over the past two decades, with the evolution and wider availability of disease-modifying therapies (DMT). MS Specialist Nurses see a range of severities of cognitive impairment, which may be more silent or under reported in relapsing remitting MS compared to progressive MS, and is very unlikely to be the presenting symptom.

Cognitive impairment can be affected by comorbidities, and has a significant impact on quality of life and independence. People often mention difficulties with verbal fluency, executive functions, multi-tasking, problems with focus or concentration, and reduced processing skills. MS Specialist Nurses need to be mindful of the factors that may mimic cognitive impairment, such as acute relapse, the side effects of DMT such as progressive multifocal leukoencephalopathy, fatigue, and low mood or anxiety. Unrelated causes such as menopause or medications such as antimuscarinics can also have similar symptoms.

Education is key to improving treatment concordance and adherence, but people with cognitive impairment may struggle to process and retain information, to understand the risk–benefit of their medication, or to remember doses and follow-up appointments. Concordance with treatment can be an issue, and MS Specialist Nurses play an important role in advocating where specific treatments may be more suitable for them. MS Specialist nurses build good therapeutic relationships with people with MS, but this may be more challenging in larger centres with larger teams and bigger caseloads, compared to a lone MS Specialist Nurse with a smaller caseload.

MS Specialist Nurses assess and evaluate patients periodically, and where appropriate can make timely onward referrals. In partnership with the multidisciplinary team (MDT), they play a role in discussing cognition early on, to educate people with MS to recognise symptoms and legitimise cognitive concerns.

For MS Specialist Nurses, knowledge about cognitive impairment is not perceived as an issue. However, challenges exist in terms of the fear of upsetting patients and their families in bringing up cognitive problems, caseload size and mix, and the burden of DMT monitoring. Virtual consultations are becoming more common for many centres, but these appointments are not suitable for all, and there will need to be a balance of face-to-face and virtual appointments.

Overcoming barriers in relation to cognitive impairment

SUSAN HOURIHAN

Occupational therapy (OT) focuses on a person, their environment and occupation, and their participation in daily life. The aim is to either restore or compensate for lost function. Occupation as a term refers to practical and purposeful activities that allow people to live independently and have a sense of identity. These can be essential everyday tasks such as self-care, work, and leisure, all of which can be affected by cognition. Work is often the place where cognitive impairment first becomes evident. OT aims to help people maintain or modify their work, or to return to work after a relapse.

In OT, formal assessment approaches are often top-down – looking first at the occupation itself, then understanding tasks and purposeful activity, and finally the component activities. This allows a break-down of where cognitive impairment may be having an impact. Functional assessments can include the Multiple Errands Test (MET), which evaluates the effect of executive function deficits on everyday functioning. Assessment of Motor and Processing Skills (AMPS) and Perceive, Recall, Plan, Perform (PRPP) can also be useful tools. A prompt and cue hierarchy can be useful to support learning modified tasks.

If a person with MS is referred to OT with a cognitive impairment already identified, they may come with a complete neuropsychology assessment. This is ideal as it allows the occupational therapist to commence with treatment, utilising cognitive strengths to compensate for weaknesses. However, frequently, people with MS will be referred to OT for treatment, such as fatigue management. In this case, they will often not have been assessed for cognitive function, despite cognitive impairment being present. There is a need to understand the stage each person is at in order to have a clear aim for optimal intervention. Ideally, OT should be performed as part of an MDT, including family and carers, with agreed goals and treatment planning.

Referral challenges from primary care and ongoing cognitive management

NASSIF MANSOUR

Currently, management and support for cognitive impairment in MS is lacking. The main symptoms of cognitive impairment in MS are short-term memory and attention deficit, problems with abstract conceptualisation, and slowed information processing. Many patients assume these symptoms are age- or fatigue-related, and do not report them to their GP – and often GPs themselves also make these assumptions and brush cognitive symptoms aside. This makes it difficult for patients with MS to get the support they need, and can be a driver of anxiety and fear around their disease and about their lives.

The lack of a diagnostic tool that could be used in primary care to flag patients with or at risk of cognitive impairment is another challenge. Even where cognitive impairment is suspected, support remains a problem. Referral to a Neuropsychologist takes 6-9 months and local Improving Access to Psychological

Perspectives from a person with MS – the lived experience

NATHALIE FRICKER

The patient voice is important in MS, and can help healthcare professionals to understand the daily experience of people with MS. From a patient perspective, physical versus cognitive symptoms are very different. There is traditionally an emphasis on preserving physical function and independence, with the mental impact a secondary consideration. Over time, cognition often declines, with difficulty finding the right words, and forgetfulness. Memory loss can mean people live more in the present – blurring a person's history and recall.

Some lifestyle changes that people with MS may make to protect themselves physically – such as stopping working or limiting activities – can perhaps accelerate the cognitive decline, as the brain is not kept active. Mental stimulation and exercise can help to combat mental decline. For example, reading and discussion in a book club can help retain vocabulary. Despite the best intentions, people naturally have bad habits and lack of discipline when trying to make lifestyle changes – and those with MS can be derailed by fatigue.

Patient experience of cognition can be variable, and is difficult to predict. The brain fog is described as a feeling of knowing you cannot find the word, which can be embarrassing and awkward. Cognitive issues are easier to hide than physical issues, and many patients do not want to admit to diminishing brain power. Although generally the world is more open-minded about disabilities and impairments, there may still be a stigma attached to cognitive impairment. However, cognitive assessments are rare in clinical practice and I personally would like to see assessments done as part of the annual review.

Therapies (IAPT) services are not specialised enough to give the necessary support required.

An important role in primary care is to help the patient acknowledge an impairment, and to understand what reasonable adjustments may be required in their life. An MDT clinic in collaboration with an MS Nurse Specialist can improve identification, support and patient satisfaction. In the future, primary-care GPs need to find ways to help patients report symptoms early, and to improve awareness and diagnosis. Early support from primary care will enable patients to access specialist services, and to live well with their MS.

Research gaps – what questions do we need to answer?

CAROLYN YOUNG

The key research gaps in the field of cognitive therapies for people with MS are the development of improved treatments which generalise to affect day-to-day cognitive function, treatment selection and individualisation for patients, and achieving consensus on the definition of 'brain fog'. In addition, better understanding is needed regarding whether different patterns of treatment are needed for relapsing and progressive subtypes, and the impact of depression and anxiety.

'Brain fog' is a term used in many chronic conditions, including cancer, coeliac disease, and chronic fatigue syndrome. Among people with MS the term 'brain fog' is used to describe myriad difficulties with memory, concentration, processing capacity or speed, and motivation. Progress requires a consensus definition of MS brain fog. In some fields, brain fog is defined as an impact on processing speed, and working, visual and verbal memory. Animal studies relating to the brain fog experienced by chemotherapy patients have identified oxidative stress and apoptosis, which inhibit neuronal proliferation and differentiation, activate microganglia, and affect chromatin remodelling. This leads to the aberrant expression of neurotrophic proteins in the brain (for review see Chemo brain: From discerning mechanisms to lifting the brain fog – An aging connection [28]). Changes have been shown in gene expression profiles, leading to the hypothesis that brain fog in chemotherapy has an epigenetic mechanism.[28,29] This raises an interesting question in MS, since many DMTs came from the world of oncology – are some cognitive effects driven by treatment, rather than the underlying disease? It will be important to answer this for future MS care.

In real-life clinical practice, clinicians want to know which form of cognitive rehabilitation is most likely to benefit an individual patient – or for service design, most patients in their practice – for a reasonable period of time. Interventions currently under investigation include music therapy, compensatory strategies, computer-based training programmes and apps. However, many studies do not use intention-to-treat analyses, and the entry criteria and study duration may not be reflective of real-world patients, or unhelpful for resource planning. In designing a cognitive rehabilitation trial, it should be clear which deficit is being treated, how it can be measured, and why it is relevant to patients, society, and payers. Trials should also record the educational level of the cohort, and state whether any of the interventions affect day-to-day functioning. More research is needed to understand how routine cognitive testing can be delivered to best benefit patients, as patients may be unwilling to undergo cognitive monitoring if there is no intervention for any deficits that may be uncovered.

Unmet needs identified via the MS Trust helpline

CLAIRE WINCHESTER

People with MS often speak about the impact of cognition problems, rather than the cognitive issues themselves. The greatest impacts of cognitive problems are on relationships, employment, and study, and can be life-altering when they are a factor in family breakdown or loss of earnings.

There are several barriers to coping with cognitive problems. Traditionally, clinical focus has been on physical problems, such as those impacting walking or dexterity. Cognitive impairment is not always regularly assessed, due to the limited time and capacity in MS services. For people with MS, the terminology around cognitive problems can be scary or difficult to accept. They may not be aware of treatments or interventions that might help them live well with cognitive problems.

People with MS particularly mention difficulties with concentration, memory and organisation, which can lead to problems absorbing and acting on information. This raises issues for health literacy, and for choosing and adhering to treatment. Cognitive problems therefore have a knock-on impact on the ability of a person to self-manage their MS effectively, and can lead to worse health outcomes.

Overall, there is not enough awareness that cognitive impairment can be part of MS, and the burden falls on the patient and their family to cope with changes and mitigate the symptoms. There is also a need to consider carers and families when assessing impact, as the cognitive decline of a loved one can be challenging to cope with. People affected by cognitive problems in MS need to know what interventions might be available, and to be supported to take positive action.

Discussion

Cognitive difficulties in MS are a significant issue, and may be experienced by 65% of people living with MS [18], but the topic can be hard to raise with health professionals. Talking about physical issues is easy for many people, but some with MS may feel they will lose a sense of themselves if they have cognitive symptoms, and this can prevent people from asking for help. Other people find it very useful to know that their symptoms are due to MS, and understanding the impact can be important in relationships and for family dynamics. Individual attitudes vary, and understanding this will guide communication and awareness in considering interventions for cognition, but demystifying cognition in MS will support many people in coming forward.

Of course, the NICE guidelines say cognition should be discussed early in the disease course, and on a regular basis [23], but in practice this does not always happen, or may be difficult to achieve. Virtual consultations have become the norm for many chronic diseases over the course of the COVID-19 pandemic, and may help to open up screening for cognition in MS – but the technology is not suitable for all. Remote delivery may be difficult for confused patients, and access may also be an issue. Where assessments are done in person, care should be taken to ensure they are delivered in optimal environments, such as asking a person to complete a single task in a quiet room [30].

Despite cognitive dysfunction being a common and disabling feature, the pathological brain changes are not fully understood [31], and precise characterisation of cognitive phenotypes is missing. Cognitive impairment is typically defined as poor performance on two or three diverse tasks, which leads to heterogeneous and ill-defined groups of people with deficits in speed, memory, or other areas [30]. However, recent research suggests defining homogeneous and clinically meaningful phenotypes may overcome some traditional limitations [32].

De Meo and colleagues have recently identified five cognitive phenotypes that may offer utility. These are preserved cognition, mild–verbal memory/semantic fluency, mild–multidomain, severe–executive/attention, and severe–multidomain [32]. Further work recently published also suggests there is a chronological sequence in which cognitive domains become impaired, with processing speed the first area affected [33]. Clinical understanding of phenotypes and sequencing may represent an important step toward personalised treatment or rehabilitation – as well as supporting understanding of the mechanism of MS-related cognitive changes [32].

Our discussions highlight several barriers to managing cognition, particularly around identification and measurement. There is agreement that measurement is important – and MS batteries are brief by neuropsychological standards – but one-on-one testing for every patient may not be practical [30]. Some people may also resist the idea of psychometric testing when it may not be possible to correct any problems that are identified, and this testing may also not make clinical sense when

that time and resource can be used in other more impactful areas. In addition, we must be careful to develop scores and assessments that can take into account a person's prior cognitive level, and an individual's cognitive needs in their daily life. It can be easy to overlook a deficit that produces a small score in a tool, but which may in fact impact the person in a very real way, for example, in their job if processing speed and memory are key elements of a role.

To improve and standardise care, there is a need to encourage a focus on cognition, and to ask about cognitive issues in people with MS. The cognition-aware healthcare professional should note discrepantly low performance and assess cognition. People with MS can be supported by presenting information in helpful ways, and monitoring disease management. Special attention should be paid to symptom management, medication adherence, and risks for falls, driving, and employment. Where needed, we should refer people to a specialist for assessment and management.

Every person – with or without MS – has a physical and cognitive reserve. The physical reserve may depend on age or fitness, but the cognitive reserve is the amount of capacity a person has to withstand insults such as relapse or atrophy, or psychological aspects such as anxiety – and still be able to function. It is possible to build up these reserves with exercise, and work is a critical factor in maintaining cognitive reserves and self-esteem.

This could be an important factor in shaping the advice given to people with MS, since at present much is aimed towards paring back work in an effort to reduce fatigue, but this could be an iatrogenic factor in cognitive decline. There is clearly still much to consider. Improved understanding of cognitive deficits will inform research into cognitive rehabilitation, which seeks to restore cognitive functioning or teach compensatory strategies to minimise the impact on quality of life [30]. To support this, a workable clinical code and more suitable tools are needed to standardise care, and developing these should be a priority. Above all, cognition should be cherished.

Areas for potential work:

- Patient and lay carer education on cognition
- Resources for healthcare professionals
- Developing an assessment that could be delivered via an app or other technology
- Developing self-management programmes for maintaining cognitive reserve
- Position statement on managing health anxiety
- Rehabilitation programmes, including optimal dosing
- Implementation and management
- Further research

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Putative autoimmune mechanisms for Acute Disseminated Encephalomyelitis (ADEM) and Guillain-Barré Syndrome (GBS) associated with SARS-CoV-2 infection

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Abstract
The novel coronavirus severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, responsible for the ongoing COVID-19 pandemic, is associated with a broad manifestation of neurological disease, including Acute Disseminated Encephalomyelitis (ADEM) and Guillain-Barré Syndrome (GBS), amongst other forms of autoimmune encephalitis, stroke, encephalopathy, delirium, and cranial neuropathies. These phenomena are not limited to human coronaviruses but are also seen in a minority of patients in response to other viral infection. There is good evidence that an autoimmune mechanism hypothesis is likely. The final pathology is probably the culmination of mixed mechanisms such as vascular and immune dysregulation as well as direct viral invasion of neurons – though there is little if any evidence of viral invasion in the literature to date. The aim of this review is to elucidate the emerging evidence about this subset of COVID-19-associated neurological disease. This unique opportunity to study the interactions between virus and host immune and central nervous system (CNS) to gain novel insights applicable to other probable autoimmune neurological disease. I have conducted a literature search as well as drawn on my own observations from the COVID-19 and encephalitis multidisciplinary meetings at Queen Square National Hospital for Neurology and Neurosurgery, London, UK.

Though rare, involvement of the CNS during or after viral infection results in serious disease. This is the case in the minority of patients with severe COVID-19. COVID-19 is the result of infection by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first identified in Wuhan, China in November 2019, causing flu-like illness in most infected patients and severe pneumonia and/or death in a minority. The emerging evidence for neurological disease during or following COVID-19 is an echo of what took place during the SARS and MERS pandemics – a spectrum of both inflammatory and ischaemic disease processes. Here I focus on ADEM-like disease (as a subset of Autoimmune Encephalitis (AE)) and GBS associated with COVID-19. ADEM is characterised clinically by the acute onset of polyfocal neurological symptoms such as pyramidal signs, ataxia, hemiparesis, optic neuritis and other cranial nerve involvement, and seizures, presenting with highest frequency in childhood [1]. GBS is a peripheral neuropathy, which presents as progressive bilateral weakness of the arms and/or legs in the absence of CNS involvement. Progression is rapid, with the majority of patients with GBS reaching their maximum disability in two weeks resulting in paresis of the limb, cranial and respiratory musculature [2]. I will discuss existing and emerging evidence supporting each of the following theories: a) autoantibody production via i) molecular mimicry or ii) other means; b) systemic immune dysregulation; and c) neuronal damage via direct viral invasion. The development of ADEM has already been linked to precedent infectious, particularly viral, disease [1] and GBS to a variety of viruses and to a number of other pandemics, such as Zika Virus, MERS-CoV and SARS-CoV [3]. It is known that autoantibody production in GBS drives axonal degeneration in pathogenesis. It is believed that both these diseases develop as the result of a similar autoimmune mechanism.

COVID-19-associated neurological disease

The spectrum of neurological disease associated with COVID-19 is broad [4,5,6,7]. A recent study of patients at Queen Square outlined 4 major categories of neurological disease manifestation [8] – encephalopathies with delirium, inflammatory CNS syndromes (including ADEM) and peripheral neurological disorders (including GBS), though vasculopathies, such as ischaemic and haemorrhagic stroke seem to dominate, which is understandable in the context of COVID-19 assoicated lung and vascular injury. They reported a 'striking' incidence of ADEM amongst their patients, which did not correlate with lung disease severity [9], suggesting that pathogenesis mechanisms of inflammatory lung and brain tissue damage differ. In support of this, some cases

of neurological disease have preceded lung disease [3]. Notwithstanding, it is known that hypoxia, the effects of systemic infection, critical illness and hypertension have been associated with encephalopathy. This puts the spectrum of COVID-19-associated neurological disease into context when considering that most patients with severe neurological symptoms have been admitted to ITU and are in significantly poor health.

Autoimmune disease via autoantibody production

Evidence supporting an autoimmune mechanism for neurological disease coincidental with SARS-CoV-2 infection comes from individual case studies with the following clinical features: a) positive autoantibody screen; and b) clinical features which resemble neurological disease of known autoimmune origin. In addition, the mere fact that COVID-19 has been associated with outbreaks of GBS [10] warrants suspicion of an autoimmune mechanism. However, there is still some controversy over whether COVID-19 is truly associated with these cases [11].

Several case studies of patients with probable AE and/or GBS have reported the detection of autoantibodies. Gutiérrez-Ortiz et al. describe the case of a patient positive for anti-GD1b-IgG and Miller-Fisher syndrome after acute SARS-CoV-2 infection. Yet in the same case report, they identified a patient with probable polyneuritis cranialis with a negative autoantibody screen [12]. In the same vein, several groups have reported anti-GM and anti-GD1b IgG positive post-COVID patients with GBS [13,14]. In most of these cases of GBS, titre of both SARS-CoV-2 and identified autoantibody was lower or not present in CSF and higher in plasma, suggestive of a mechanism involving autoantibody production outside of the CNS and excluding one which involves SARS-CoV-2 interacting with the privileged immune system of the CNS. In terms of ADEM, Grimaldi et al. describe the case of a patient who was positive for autoantibodies to the nuclei of Purkinje cells, striatal and hippocampal neurons in CSF and plasma, though the identity of the specific antigen involved was unknown and the synthesis of these autoantibodies has not been reported in any other case of autoimmune encephalitis [15]. Another case showed positive CSF examinations for NMDAR and GFAP antibodies [16].

It is important to highlight that the majority of cases of ADEM and GBS report negative broad immunological screens in CSF and serum (for autoantibodies against Caspr 2, LGi1, NMDAR, anti-Hu, anti-GAD, anti-aquaporin 4 and anti-DPPX) [8,17,18,19,20]. The fact that most GBS and AE cases associated with SARS-CoV-2 are seronegative does not rule out an autoimmune mechanism. The literature on probable seronegative neuroautoimmune disorders is established and may reflect the situation for SARS-CoV-2-associated autoimmune disease [21]. It is thought that pathogenesis in seronegative patients with clear autoimmune disease either results from the production of an undetected or uncharacterised autoantibody, or that pathogenesis is wholly different and not dependent on autoantibody production. Firstly, there are subtypes of GBS for which no specific autoantibody has yet been discovered, in addition to well-known autoantibodies for GM1, GD1a, GA1Nac-GD1a, GD1b and GQ1b ganglioside antibodies, which could explain why recent case studies of GBS in the context of COVID-19 show either no CSF abnormalities or a mixture amongst patients, as described previously [3,8,15,22,23,24]. Antibody detection in cases of GBS in association with Zika virus have been equally poor as for AE in COVID-19 [25]. Interestingly, Zhao et al. describe the first reported case of GBS in coincidence with COVID-19 before the manifestation of typical symptoms and RT-PCR detection of SARS-CoV-2 on nasopharyngeal swab [24]. This suggests a para-infectious rather than post-infectious disease process, which is in agreement with other studies which report the temporal coincidence of neurological symptoms with fever, myalgia and other typical 'early' COVID-19 symptoms [8,26].

In support of the latter possibility that COVID-19-associated GBS and AE result from different disease mechanisms, infection-triggered autoantibody production does not always result in clinical disease: for example, in a follow up study of HSV encephalitis patients, whilst 27% went on to develop anti-NMDAR autoimmune encephalitis, 3 patients synthesised anti-NMDAR autoantibodies asymptomatically [27]. Further, Keddie et al. found no significant similarities between the SARS-CoV-2 genome and human genome, suggesting that molecular mimicry – a typical mechanism of virus-mediated autoantibody production, particularly in GBS – might not be taking place [11]. Immune hyperactivity or 'cytokine storm syndrome' (CSS) are involved in the manifestation of COVID-19-associated neurological disease in general [28]. Numerous cases of GBS and ADEM show the typical screen of elevated cytokines characteristic of CSS. Therefore, it is likely that a combination of mechanisms starting with systemic SARS-CoV-2 infection take place to result in autoimmune disease. These mechanisms manifest heterogeneously amongst patients depending on individual factors, such as genetics. For example, it has been shown that a number of HLA phenotypes predispose to COVID-19-associated GBS [29].

Autoimmune-like clinical features

Brain imaging of COVID-19 brain disease frequently shows pathological lesions that are also characteristic of ADEM and AHLE [30]. Paterson et al. describe the typical radiological presentations of ADEM-like COVID patients: multifocal white matter hyperintense lesions on FLAIR, in association with haemorrhagic lesions in some - in the Queen Square study, 8 out of 43 patients had vascular or microvascular presentations but the high incidence of haemorrhagic changes on imaging across all categories of neurological disease were startling [8,31]. Furthermore, other biopsy studies show some signs of ADEM-like histological appearance: small white matter lesions with clusters of macrophages with variability in axonal injury and perivenular association [32]. But histopathological findings in one patient with white matter microbleeds showed lymphohistiocytic inflammation, suggestive of cytokine storm-induced lymphocyte recruitment [33] - it is not entirely clear whether white matter changes seen in imaging and histopathology studies are secondary to vascular insults or the result of immune-mediated demyelination, and whether this occurs downstream of autoimmune disease or is a primary dysregulation of the immune disease in its own right [34]. It is widely known that inborn toll-like receptor 3 (TLR3) mutations cause Herpes Simplex Encephalitis (HSE) as a result of inappropriate immune response to Herpes Simplex virus 1 (HSV-1) [35]. It is possible that encephalitic disease can originate at the level of the immune system and that, perhaps, COVID-related disease shares some aspects of this. Plus, it is well-known that levels of pro-inflammatory markers, such as IL-6 in particular, increase with disease severity [36] and that several genetic polymorphisms responsible for physiological immune function have been associated with COVID-19 susceptibility [37]. These patients also have higher numbers of FCN1+ macrophages in the airways as well as CD14+CD16+ monocytes in peripheral blood smears, which are responsible for the supposed CSS which causes extreme disease and even fatality in COVID-19 [28]. Pilotto et al. report a case of COVID-19 associated encephalitis where the patient was CSF-negative for SARS-CoV-2 but with a high level of IL-8 and TNFα in the CSF [38]. It is these high levels of circulating cytokines which result in systemic disease and may be equally important in the context of neurological disease manifestation. It is possible that final observed pathology is a combination of disease processes occurring simultaneously. This would explain the broad spectrum of COVID-19 associated neurological disease.

This combination of pathogenic mechanisms could arise through a 'multiple hit' manner, where consecutive immunological challenge, resulting in autoantibody production or otherwise, results in disease. In support of this, Panariello et al. report the case of a psychotic patient with a history of substance use disorder – it is known that exogenous substances such as ketamine can induce anti-NMDAR encephalitis [39] – with clinical signs of COVID-19 and no response to antipsychotics. Upon worsening encephalitic symptoms, CSF analysis revealed anti-NMDAR antibodies and a diagnosis of anti-NMDAR autoimmune encephalitis was made [16]. It is possible that COVID-19 and the spectrum of its systemic and immune effects, such as CSS-type effects, provided the final step to bring this particular patient to disease threshold. This would also explain why a subset of COVID-19

patients present with GBS and ADEM after a delay [40], as is the case with a range of neuroautoimmune diseases which result from secondary autoantibody production upon immunogenic challenge of multiple epitopes.

Neuronal damage via direct viral entry

On the other hand, it is argued that rather than causing classical autoimmune disease, SARS-CoV-2 causes neurological damage by directly invading the CNS. SARS-CoV-2 is a cytopathic virus, meaning that it gains entry to host cells – via ACE2 and TMPRSS2 surface receptors - and induces cell death and injury. A contradiction to the autoimmune hypothesis for ADEM is the presence of SARS-CoV-2 in the CSF and biopsy samples in a number of case studies [41], though rarely in cases of GBS [20]. Moreover, it has been posited that SARS-CoV-2, like SARS-CoV, has neuroinvasive potential and spreads to the CNS via the olfactory bulb and nerve through the cribriform plate and olfactory epithelium, accounting for the widespread reporting of symptoms of anosmia and hyposmia amongst COVID-19 patients [42]. The expression of ACE2 on olfactory epithelia and, further, reported in areas of the brain by several studies, suggest that the virus can directly infect a wide range of neurons.

SARS-CoV has been reliably extracted from autopsy specimens of patients who died as a result of SARS, in particular in neurons of the cortex and hypothalamus, and ACE2 is strongly expressed in the ventrolateral medulla and the nucleus of the tractus solitarus [41]. Similarly, histopathology studies of COVID-19 patients found neuronal cell loss and axonal degeneration in the dorsal motor nuclei of CN X, CN V, nucleus of the tractus solitaris, the dorsal raphe nuclei and fasciculus longitudinalis, though it is difficult to say whether these widespread neuronal insults were the result of direct viral infection or an immune response.

However, evidence of viral CNS entry by analysis of CSF across case studies has proven inconclusive: none of the patients in the Queen Square study had tested positive for SARS-CoV-2 RT-PCR CSF and data is mixed amongst other studies [4,9,36,43,44]. Moreover, treatment for COVID-19 with antivirals has been discontinued following advice from the WHO, with reports conflicting over their efficacy. But, a single case study of probable acute encephalitis in association with SARS-CoV-2 and positive CSF result has been reported, which should lead us not to undermine the neuro-invasive potential of this virus [9].

Conclusion

Whilst I argue for an autoimmune-mediated mechanism, or at least an autoimmune trigger to detectable disease, there is a great amount of conflicting evidence in support of several different hypotheses, namely viral infiltration or a broader systemic 'cytokine storm'. Rather than being competitors, it seems likely that these mechanisms must be non-exclusive and must add up uniquely within each patient, accounting for the variability in neurological presentation in association with COVID-19. Such a collaboration of disease processes would explain why outcome also differs so much between individuals of different ethnic groups, ages, and past medical history. The implication for a multifactorial pathogenesis is that there may be no universal effective treatment. It is therefore imperative that neurological cases associated with COVID-19 are examined with care to understand if one mechanism dominates. This could, for example, either guide treatment towards steroidal agents for a CSS-dominant pathogenesis or intravenous immunoglobulin therapies to treat autoantibody-dominant mechanisms. Encephalitis Lethargica (EL) so-called postencephalitic parkinsonism which take decades to manifest itself and is estimated to have affected 1 million people between 1915 and 1930 [45]. The highly elusive relationship between the influenza pandemic of 1916-1918 and the EL pandemic should prompt us to question the role of viral infection in long-term neurological disease. Whilst it is currently hard to both dissect the true relationship between COVID-19 and neuroautoimmune diseases, and to predict what is to come following COVID-19, our understanding of its neurological effects will be crucial in preventing a similar outcome.

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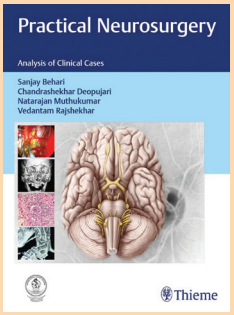
Practical Neurosurgery. Analysis of Clinical Cases



Authors: Sanjay Behari, Chandrashekhar Deopujari, Natarajan Muthukumar, Vedantam Rajshekar
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With the changing face of modern hospital medicine and increasing demands on our time, education for surgical trainees has been driven towards easy access resources and small succinct handbooks, to provide us with quick answers on a given topic. As the authors of this book suggest in the preface, the skills of history and examination, exploratory ward round discussion and diagnostic reasoning has also been diminished due to time constraints. The authors aim to remedy this with their book by providing a 'problem-solving approach' to a broad spectrum of neurosurgical presentations, for example, 'a patient with facial pain'. Targeted at junior trainees, this problem-solving approach aims to stimulate analysis of clinical scenarios and guide subsequent management of cases we may be confronted with on a day to day basis.

The book is divided into four sections – in (intra-)cranial, cranial nerves, neuroendocrine (and phacomatoses) and spine and brachial plexus. Traversing the four broad sections are 52 chapters covering a plethora of both neurosurgical and more general neurological presentations – a patient with anosmia, a child with precocious puberty, a patient with monoparesis and so forth. Despite the four overarching sections, there is some lack of cohesion between chapters; the style (and quality) varies over the course of the book.

The opening four chapters of the cranial section concern paediatric problems; a child with a large head, a child with ataxia and vomiting, a child with abnormal head shape and a child with a swelling on the forehead and increased distance between palpebral fissures. The opening chapter is a slow start, with repetition within the text and poor-quality images which do little to support the text. In the second chapter the image quality remains an issue, but you unexpectedly discover a relevant overview of paediatric posterior fossa brain tumours, with substantial supporting information in tabular form. The third and fourth chapters are shorter, with better image quality and more appeal for the visual learner. The chapters then progress to cover basic concepts of dementia, seizures and lobar signs suitable for junior trainees until we reach a disappointing Chapter 10, a patient with a sudden severe headache. This provides an unstimulating chapter with failure to highlight the importance of timing when performing a lumbar puncture in suspected subarachnoid haemorrhage and no guidance on clinical management, raising questions as to the target readership of the book.

The erratic first section settles down, however, to a steady stream in the next chapters. These provide well-judged explanations of essential neuroanatomy and appropriate use of appropriate diagrams. Many chapters conclude with further reading tips but these suggestions are rather varied in quantity and quality, and are sometimes omitted.

Chapter 13 commences the cranial nerves section, with simplified visual explanations of cranial nerve physiology and relevant pathology pertaining to each chapter title, with the exception of chapter 22 (a patient with a stiff neck – a simple-sounding title which leads to coverage of jugular foramen syndromes). A case-based style discussion is introduced in chapter 14, a patient with cerebellopontine angle syndrome. This chapter provides the reader with useful exam-style questioning. The latter half of this chapter is focused on surgical techniques, offering engagement and self-assessment for higher surgical trainees.

Chapters 25 to 30 cover neuroendocrine conditions and phacomatoses. This shortest section of the book is perhaps the easiest to read, with endocrine pathology being well-suited to the book's format, and content matching well to each chapter title.

The final section is then the longest, covering spine and brachial plexus. It again contains a mixture of anticipated and hidden information within the chapters; the rather chaotic style of the first cranial chapters seems to creep back in. The latter part of this section includes some miscellaneous chapters. Some might have been better placed elsewhere (e.g. the patient with fundoscopic abnormality could have been placed in the cranial nerves section).

The majority of authors practice in India, as a result, certain pathologies are given more weight than if written from UK institutions. However the authors have done well to make this engaging and applicable to all neurosurgical trainees. With a few exceptions, the chapters provide information for all stages of training.

This is not a standalone book for trainees and will not supersede volumes such as Greenberg's or Samadouras, which provide quick delivery of information. But as laid out within its preface, it does not try to. Once familiar with the leisurely pace, and the use of repetition, it can provide pleasant (perhaps passive) revision from being picked up to read individual chapters.

Neurological literature: Headache 10

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Those familiar with neurological consultations will know from experience that patients referred with headache may sometimes (but not always!) struggle to describe their symptoms, requiring some semi-structured promptings from the clinician to draw out the salient features (it makes no sense, conceptually, to speak, as some do, of "featureless" headaches).

Many years ago, the Neurologist JN ("Nat") Blau (1928-2010) reported that in his clinics most patients (70%) spoke for two minutes or less when invited to describe their symptoms, indeed 42% spoke for less than 1 minute [1]. Although not all were headache patients (although that was Blau's area of specialist interest, and some of the patients were seen in a dedicated migraine clinic), the findings may nevertheless support the idea that, without interruptions or promptings, patient accounts are generally brief. It would be interesting to know, more than 30 years after Blau's report, if this is still the case.

Blau noted that those with experience of speaking in public spoke the longest. How might professional writers, whose metier is dependent on words, describe headache?

Previous instalments in this series of occasional pieces published in *ACNR* (and now conveniently collected elsewhere [2]) documenting accounts of headache encountered in literary or biographical material have provided some examples, but whether or not these are based on personal experience, or simply products of the writerly imagination, is seldom disclosed.

AS Byatt (b. 1936) won the 1990 Booker Prize for her novel *Possession* [3]. In a correspondence purportedly dating to the mid-nineteenth century, one of the characters, Christabel LaMotte, reports to the poet, Randolph Henry Ash,

> I write to you from an unhappy House … for I have an invalid dependent upon me – my poor Blanche – quite *racked* with hideous headaches – and nausea – quite prostrated – and unable to pursue the work which is her life. … she is too ill and cannot go on. I am not in much better case myself – but I make *tisanes*, which I find efficacious. (172-3)

Christabel's correspondent responds:

> I do have the clearest olfactory ghost of yr [sic] tisanes – though they hesitate between verveine and lime and raspberry-leaves, which my own dear mother found most efficacious in case of headache and lassitude. (177)

Tisanes are herbal teas, made from the infusion or decoction of herbs, spices, or other plant material. Verveine, or vervain, also known as lemon verbena, is a type of herbal tea. Other literary examples of tea used as a headache treatment may be noted, for example in Jane Austen's *Mansfield Park* (1814), and in Thomas Mann's *Doctor Faustus* (1947) where "real strong tea made real sour with lots of lemon" is suggested.

Christabel later reports to Ash that:

> I see whole bevies of shooting stars – like gold arrows before my darkening eyes – they presage Headache … The headache proceeds apace. Half my head – is merely a gourd full of pain. (194-5)

In the novel, these old letters only come to light in the late twentieth century when two academics, respectively researching LaMotte and Ash, collaborate. They also view the journal of Ash's wife, Ellen, who, it turns out, also had headaches:

> June [1859]
> I felt a headache coming on … I retired to my room and slept for two hours, waking somewhat refreshed, though with a vestigial headache. (227)

> A worse day. The headache seized me and I lay all day in a darkened bedroom, betwixt asleep and wake. There are many bodily sensations that are indescribable yet immediately recognisable … which could never be conveyed to one who had no previous experience of them. Such is the way in which the preliminary dizziness or vanishing incapacitates the body and intimates the headache to come. It is curiously impossible – once entered into this state – to imagine ever issuing out of it – so that the Patience [sic] required to endure it seems to be a total eternal patience. Towards evening it lifted a little.

> Worse still. Dr Pimlott came and prescribed laudanum, which I found some relief in. (230)

Much of the typical migraine symptomatology is to be found in these letters and journal entries: their severity, accompanying nausea and visual symptoms, hemicranial involvement, interruption of occupational function, recourse to treatment. All contribute to the authenticity of the account. The report that these "sensations … could never be conveyed to one who had no previous experience of them" might be pertinent to the brevity of patients' accounts of their headache symptoms (and also of other neurological symptoms).

> Interestingly, Ellen Ash's sister, Patience, also complains of "incessant … headaches" (225).

A family history of migraine is, of course, not uncommon, and may be associated with a lower age of onset [4]. As is well-known, AS Byatt's younger sister, Margaret Drabble (b. 1939), is also a writer. If we accept the premise that AS Byatt is writing from personal experience of migraine with aura in *Possession*, it might be interesting to know if her sister may be similarly afflicted, perhaps assessed by any

reference to headaches in her literary works.

Although I claim no familiarity with Drabble's extensive oeuvre, I think there is some subtle evidence to answer this question. For example, in what may be her first written short story, *A Pyrrhic victory* (although not the first published, appearing in 1968) [5], the central character, Anne, is described at the outset as "exhausted: her head ached with the sun, she felt both sick and hungry" (49). In *A day in the life of a smiling woman* (1973), the title character, Jenny Jamieson, has a headache when tired on returning late from her work one evening (111). In *The merry widow* (1989), an offstage character, Harriet, is described as "always ill … what stories of migraines" (151). No detailed account of symptoms is provided in any of these passing references.

Despite featuring scenes set in both primary and secondary medical care settings, no headaches occur in Drabble's novel *The millstone* (1965). However, in *Jerusalem the golden* (1967) [6], the central character, Clara Maugham, a student in London, encounters the Denham family, whose attitudes and behaviour differ greatly from her own restricted upbringing in "Northam". At the end of a visit to the Denham household in Highgate, Clara "began to feel a sense of overwhelming fatigue. Her head ached … her mind would no longer pay attention. Whole concepts, whole reorganizations of thought swam drunkenly through her head … when she got home she was suddenly and violently sick" (106). Subsequently Clara finds that "she grew accustomed to leaving their house with a headache" (107) and later discloses that this was because the experience was "so marvellous I couldn't take it" (167).

These brief descriptions of headache in some of Drabble's works may lack the richness of the material in Byatt's novel, but nonetheless suggest a familiarity with headache symptomatology. The brevity of Drabble's portrayals may be typical of patient accounts before the clinician draws out additional details. To paraphrase, it may indeed be the case that even with the word skills of a professional writer "many bodily sensations … are indescribable" and cannot therefore "be conveyed to one who had no previous experience of them".

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Cerebral malaria and the story of Quinine and the Fever Trees

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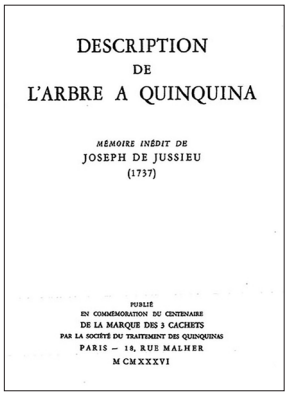
Abstract

Cinchona bark was first recorded as a cure for malaria by the Spanish in Peru around 1630. A Spanish missionary allegedly learned of the treatment from the Indian natives. Cerebral malaria caused by *Plasmodium falciparum* is life threatening and one of the commonest encephalopathies in the world. Quinine was the first effective treatment, discovered in the bark of *quina-quina*, cinchona, 'the fever tree' in Peru in 1633. Many tales – many fanciful – relate to its early use. Foremost of the discoverers in 1735 was a group of French scientists in an expedition to Peru directed by the Parisian *Academie Royale des Sciences*. It was then widely exported and employed in Spain, Italy and Britain to become the standard treatment.

From its first recorded use to cure malaria by the Spanish in Peru around 1630, the history of Cinchona bark is a mixture of facts and legend.

Cerebral malaria caused by *Plasmodium falciparum* is one of the most common encephalopathies in the world. In 2017 mal-aria (Italian: bad air) caused an estimated 435,000 deaths (WHO). Female Anopheles mosquitoes transmit Plasmodium falciparum sporozoites via the blood then enter the liver where they mature into schizonts, which multiply into merozoites and invade and burst erythrocytes; they are sequestered in deep vascular beds causing petechial haemorrhage and cerebral oedema [1,2]. Coma, epileptic seizures, retinopathy and brainstem symptoms due to raised intracranial pressure and oedema are the salient clinical features. Quinine was the most effective treatment until artemisinin derivatives were discovered.

Quinine was an active agent in one of the first cures for fevers, the bark of *quina-quina*, cinchona, 'the fever tree' and was described by Fra. Antonio de1a Calancha, an Augustinian missionary. In Lima in 1633, he wrote: 'the fever tree is made into powder and given as a beverage, cures the fevers


DESCRIPTION
DE
L'ARBRE A QUINQUINA

MÉMOIRE INÉDIT DE
JOSEPH DE JUSSIEU
(1737)

PUBLIÉ
EN COMMÉMORATION DU CENTENAIRE
DE LA MARQUE DES 3 CACHETS
PAR LA SOCIÉTÉ DU TRAITEMENT DES QUINQUINAS
PARIS — 18, RUE MALHER
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Figure 1

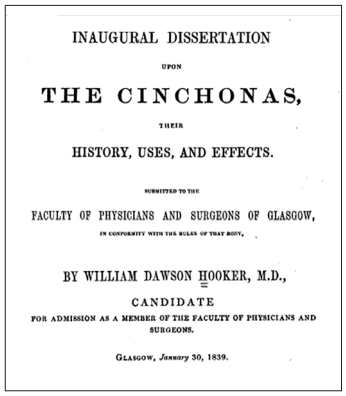
INAUGURAL DISSERTATION
UPON
THE CINCHONAS,
THEIR
HISTORY, USES, AND EFFECTS.
SUBMITTED TO THE
FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW,
IN CONFORMITY WITH THE RULES OF THAT BODY,
BY WILLIAM DAWSON HOOKER, M.D.,
CANDIDATE
FOR ADMISSION AS A MEMBER OF THE FACULTY OF PHYSICIANS AND SURGEONS.
GLASGOW, January 30, 1839.

Figure 2

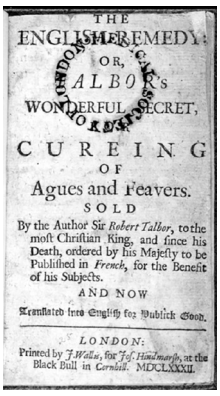
THE
ENGLISH REMEDY:
OR,
ALBO's
WONDERFUL SECRET,
CUREING
OF
Agues and Feavers.
SOLD
By the Author Sir Robert Talbor, to the most Christian King, and since his Death, ordered by his Majesty to be Published in French, for the Benefit of his Subjects.
AND NOW
Translated into English for Publick Good.
LONDON:
Printed by J. Wallis, for Jos. Hindmarsh, at the Black Bull in Cornhill. MDCLXXXII.

Figure 3

Figure 4

and tertians;' the tree grows in Loja [Loxa], Peru [3,4].

Cinchona bark derives from several species and hybrids of Cinchona trees (*Rubiaceae*), indigenous to Colombia, Ecuador, Peru and Bolivia. In the 1640s, Cardinal Juan de Lugo, a Spanish missionary allegedly learned of the treatment from the Indian natives and brought it to Spain (publishing his *Schedula Romana*,) where it was known as *Cardinal's powder* [5]. Pedro Barba, Professor of Medicine in Valladolid, in 1642 first commended cinchona bark for the cure of tertian ague.

In 1735, the French scientists (Louis Godin, Pierre Bouguer, Joseph de Jussieu, (Figure 1) and the naturalist and mathematician Charles-Marie de la Condamine) led an expedition to Quito in Peru (now Ecuador) directed by the *Academie Royale des Sciences* in Paris. Its main purpose was to measure precisely one degree of latitude at the equator that would enable them to verify the shape of the earth, because Newton in *Principia* 1687 had controversially argued that it was an oblate spheroid – a sphere, squashed at its poles and swollen at the equator.

This expedition of French scientists was fraught with illness, deaths and much internal dissension. It was not completed until early 1743. After disputes with his colleagues, La Condamine set off alone through danger-ridden dense rain forests to head for Quita. On the way he encountered natives who told of an ancient tradition of the Andean natives, who successfully used bark, locally called cascara de Loxa from the *arbol de la cascarilla* (cinchona or China) [3] trees [6] to treat their fevers. Many apocryphal and fanciful stories are recorded of cures by native Indians for agues and fevers [4]. They recognised three species, the most effective one characterised by its red bark [5,7]. It is however, unlikely that native Indians used this remedy, for Hooker's dissertation (Figure 2) later claimed:

> *Native Indians never will use the Cinchona as a remedy, but consider it as a medicine producing gangrene and death: they prefer an almost certain natural death to what they consider as poisoning themselves [8].*

La Condamine published his botanical work in 1738 [9]. Cinchona became known as the Peruvian, Jesuit's bark, or the Countess's powder. Another improbable legend relates that the Spanish Countess of Cinchón, the wife of the Viceroy of Peru, in 1638 became ill with intermittent fever in the palace of Lima. Don Francisco Lopez de Canizares, the Corregidor of Loxa (who had been cured of fever by the same drug), gave the powdered bark to her physician, Juan de Vega. The countess recovered rapidly and ordered its widespread distribution [6]. Carolus Linnaeus (1707-1778) gave the name Cinchona to the quina-quina tree. His misspelling of the Countess's name has continued [10].

When Cinchona was transported to Spain, Italy and Britain its medicinal value was much argued since the separation of malaria known as tertian fever from other agues was far from precise. Thomas Sydenham (1624-1689) in his *Methodus Curandi Febris* (1666) emphasised its value in malaria and Willis observed it in daily use, although malaria was thought to be rare in Britain at the time. The more general introduction of cinchona bark in England has been attributed to Robert Talbor (Figure 3), who in 1671 made his fame and fortune exploiting his 'secret remedy.' Though a medically unqualified apothecary, he successfully treated the fever of Charles II and in 1672 was appointed physician to the King, and was later knighted. In 1677 cinchona first appeared officially in the London Pharmacopoeia as *Cortex Peruanus*.

Two hundred years later, Pierre Pelletier and Joseph Caventou (Figure 4) isolated quinine alkaloid from the bark in 1820 [11]. Cinchona contains Quinine, and other alkaloids: quinidine, cinchonine and cinchonidine. Each has rapid schizonticide activity against the erythrocytic forms of Plasmodium species. Synthetic antimalarials were developed and chloroquine became the drug of choice. Chloroquine-resistant strains of P. falciparum developed and are now treated with artemisinin derivatives: artesunate (C19-H28-O8) and artemether. Artesunate is currently the treatment of choice for falciparum malaria.

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The 2021 International Linked Clinical Trials Meeting

The International Linked Clinical Trials (iLCT) programme is the flagship drug repurposing initiative of Cure Parkinson's and Van Andel Institute (VAI) focussed on identifying and clinically testing already available drugs that show potential to slow, stop or reverse the progression of Parkinson's.

Every year the iLCT committee, of over 20 Parkinson's specialists, meets to discuss the progress of current iLCT clinical trials and importantly, debates a set of newly collated dossiers outlining current medical knowledge on a range of novel treatments which show potential for Parkinson's. Once drugs are prioritised by the committee, Cure Parkinson's is mandated to then take them into clinical trials.

The pandemic has meant that the recent iLCT meetings have been virtual, however this has not diminished the determination and enthusiasm of the committee members to progress their objectives. The committee met in October and prioritised new drug candidates to move to clinical trials.

Approximately half of the dossiers assessed at the recent meeting were of novel therapeutics that are being developed by biotech companies (under strict non-disclosure conditions) . The remainder focused on molecules that offer potential to be repurposed in clinical trials for Parkinson's.

In summary, five agents were prioritised by the committee at this iLCT meeting; Cure Parkinson's will now focus all effort into advancing each of these into clinical testing.

Here, Dr Simon Stott presents his 2021 update on current iLCT trials and those about to begin.
https://youtu.be/rlKxAs2Mlhg

https://cureparkinsons.org.uk

World Congress of Neurology 2021

Conference details: 3-7 October 2021. Conference streamed virtually. ***Report by:*** Anomali Shilpika Vidanagamage, Senior Clinical Fellow in Neurology, St Georges University Hospital, London, UK. ***Conflict of interest statement:*** None declared.

The 25th World Congress of Neurology (WCN) occurred virtually from October 3rd to 7th 2021. The biennial conference was organised by the World Federation of Neurology (WFN) in association with the Italian Society of Neurology (SIN). It was the first-ever virtual congress with the attendance of 4500 participants from 120 countries. The conference was originally scheduled in Rome, Italy.

Dr Antonio Federico, President of WCN 2021, welcomed everyone on behalf of WFN and SIN on the e platform. The title of this congress was "Inspired by the past to build the future of Neurology" as Italy and Rome were the origins of many Arts and histories.

As a consequence of the travel restrictions from the pandemic, this was the first time that the WCN was held in an entirely online environment yet retained the local flavour. The fully personalised interactive virtual platform was created with a unique Italian flavour, based on the ancient Roman amphitheatre colosseum allowing the virtual user to enter the theatre and choose a preferred venue to attend.

The exceptionally exciting and diverse scientific programme was presented live and on-demand allowing participants for the first time to take part in all scientific sessions. The congress consisted of 77 scientific sessions and 45 teaching courses delivered by 277 speakers and there were numerous presidential and regional symposia. All the sessions were very interactive collaborating with thousands of peers across the world.

The World Congress of Neurology brings together leading neuroscientists and public health experts to turn research into action and emphasise the importance of brain health across the globe. This year, numerous landmark research findings were unveiled at the sessions.

New developments in the field of blood biomarkers for brain diseases including traumatic brain injury (TBI), and neurodegenerative diseases such as Alzheimer's were brought up. The work of world-renowned Neuroscientist, Henrik Zetterberg, Professor of Neurochemistry, University of Gothenburg, Sweden, was presented at the congress. "Within the last five years, measurement techniques for biomarkers have become much more sensitive. We have seen a 500- to 1000-fold improvement in analytical sensitivity when we measure molecules that change in the brain of someone with Alzheimer's disease, stroke, traumatic brain injury (TBI) or other brain diseases," said Zetterberg.

This improvement in data analysis has led to the development of several tests that can detect both general neuronal activity and brain changes related to Alzheimer's disease and other neurodegenerative dementias. Such tests include blood tests to measure neurofilament light chain in either TBI or Alzheimer's disease, phosphorylated-tau-181 (ptau 181) and beta-amyloid protein in Alzheimer's disease and a test to detect activation of astrocytes in brain damage. "These tests can help diagnose a brain injury as well as help determine when the brain has healed. For example, a sports player who experiences a concussion may receive a neurofilament light blood test to help determine if they are ready to return to playing or if they should remain on the side-lines for longer," said Zetterberg. Although this research would not result in cures for TBI or neurodegenerative disease, it will hasten the development of drug treatments and assist in clinical trials in the fields.

Dr Antonio Federico – President of WCN at the Welcome address.

Gero Miesenböck, Waynflete Professor of Physiology at the Centre for Neural Circuits and Behaviour, Oxford, England presented very interesting research on brain mechanisms that regulate sleep on 5th October 2021. He stated that the function and the biology of sleep are largely unknown and solving the mystery of sleep will help to cure many diseases. His research found that one particular ion channel in the sleep-inducing cells of fruit flies is crucial for turning sleep need into sleep. Determining how this mechanism works may lead to new therapies for sleep problems. "If I had to summarise my presentation in a single catchphrase, I'd say that sleep is an antioxidant," said Miesenböck.

The 9th WCN Tournaments of the minds, as always, was very competitive and mind-blowing.

Performing the tournaments of minds on a virtual platform with attendees from different parts of the world would have been a huge technical challenge that was well handled. The team Kerala Institute of Medical Sciences of India won the trophy for 2021 and the team GB Pant Hospital in India were the runners up.

Through the poster gallery, a delegate could go through the e posters presented and the presenters were allowed to arrange chat rooms to discuss their research. The networking lounge allowed delegates to communicate with each other, on an e platform, which helped to build up fellowship.

The timeless magic of the eternal city of Rome could be felt virtually by exploring virtual tours to historical places in Italy. This brought much liveliness to the conference.

The World Congress of Neurology acted as a platform to raise global attention on the looming burden of neurological disorders. In his presidential plenary address, WFN President Prof. William Carroll discussed the origins, goals, and progress of the Intersectoral global development action plan on Epilepsy and other neurological disorders (IGAP). For the first time in its history, the World Health Organization (WHO) is recognising the need to focus on neurological diseases and disorders around the world, especially in under-resourced countries. The action plan seeks to address the challenges and gaps in providing care and services for people with epilepsy and other neurological disorders that exist worldwide and ensure a comprehensive, coordinated response across sectors.

The 8th World Brain Day was commemorated along with the congress in association with Multiple Sclerosis International Federation. The theme of this year's World Brain Day is "Stop Multiple sclerosis". Prof William Carroll in his speech highlighted that; MS affects 2.8 million people of all ages globally and someone somewhere in the world receives this life-altering diagnosis every five minutes. Disease-modifying therapies to treat MS are still unavailable in many parts of the world, where there is a vast discrepancy among low income to high-income countries. It was revealed that none of the low-income countries has access to any of the disease-modifying treatment. Professor Carroll further emphasised that we can stop MS by diagnosing earlier, providing better access to treatment, and advocating for improving quality of life.

All sessions including those that were streamed live, can now be viewed on-demand until 7th January 2022. The next exciting event of WCN 2023 will be in Montreal, Canada.

WCN 2021 was a great experience with so many educational resources and food for thought. Being virtual, it was convenient and continuously useful as all the sessions and teaching courses are available to be referred to on demand. But I would honestly say I missed being in Rome in person, recollecting the experience of WCN meetings before.

Pioneering education in Lewy body dementia

Conference details: 4 November, 2021, Belfast, Ireland. ***Report by:*** Charlie Peel, Neurology Academy and Professor Iracema Leroi, Associate Professor of Geriatric Psychiatry at Trinity College Dublin & Faculty, Global Brain Health Institute, and founder of Dementia Academy, Lewy Body Academy and lead faculty of the Alzheimer's MasterClass. ***Conflict of interest statement:*** Charlie Peel, corresponding author, is a health writer for Neurology Academy; Prof Iracema Leroi is Associate Professor of Geriatric Psychiatry at Trinity College Dublin & Faculty, Global Brain Health Institute, and founder of Dementia Academy, Lewy Body Academy and lead faculty of the Alzheimer's MasterClass.

Figure 1: The Lewy body MasterClass - delegates and speakers.

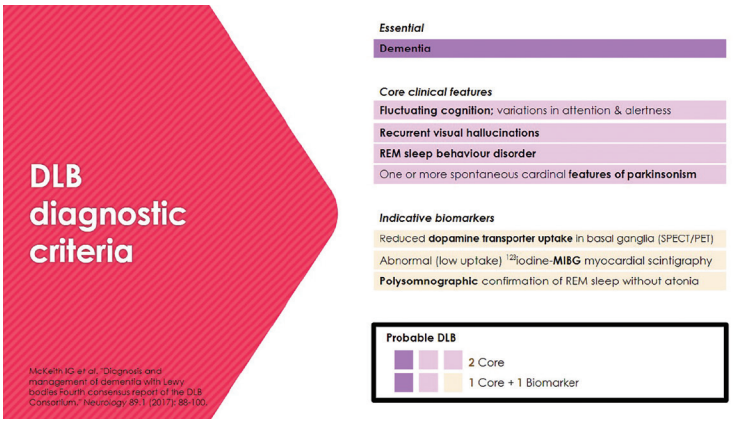

Figure 2: The diagnosis algorithm presented by Joseph Kane adapted from McKeith IG et al. (2017) [3].

On Thursday 4th November, experts in Lewy body dementia and a range of healthcare professionals keen to expand their understanding of the condition met in Belfast for the inaugural MasterClass of the new Lewy Body Academy. Part of Neurology Academy's educational umbrella, the Lewy body MasterClass was offered over a full day with a networking dinner the preceding evening. The course was partially supported by an educational grant from the Lewy Body Society [1] and was delivered in collaboration with Lewy Body Ireland [2].

Meeting a need: Education in Lewy body dementia

Lewy body dementia (LBD) and Parkinson's disease dementia (PDD) together account for up to 15% of all dementias. Recognition and management of these dementias, though, is often suboptimal, and people living with them can fall through the gaps in care. The cost of care of LBD is among the highest of all types of dementia, and the care burden is significant.

The urgent need to address the gap in awareness and clinical skills around the diagnosis and management of LBD by clinicians in the UK and Ireland prompted Professor Iracema Leroi, who founded Dementia Academy five years ago, to establish Lewy body Academy in partnership with an expert faculty and voluntary sector organisations. Its aim is to deliver bespoke education on dementia with Lewy bodies, improving detection, diagnosis, and management - and closing the gap in care.

The MasterClass

The MasterClass was aimed at clinicians working with older adults at risk of, or living, with dementia. Twenty-nine Geriatricians, Old Age Psychiatrists, Neurologists, Clinical Nurse Specialists and Allied Health Professionals attended the in-person meeting (Figure 1).

The programme featured a range of expert speakers and delved deeply into Lewy body dementia pathology, assessment, diagnosis and management with the latter given essential context and clarity by speakers with lived experience of the condition.

Utilising mixed teaching methods across didactic lectures and case-based group discussions, the sessions all drew on the latest in both research and clinical practice and ensured that each delegate was equipped with practical knowledge to implement in their own local services.

Programme highlights

Academic Clinical Lecturer Dr Joseph Kane began the course with a succinct and clear scene-setting. Peppered with practical advice, his discussions of the diagnosis algorithm (Figure 2), treatment strategies, and practical ways to approach conversations around possible REM sleep behaviour disorder were highlights for many.

Prof Dag Aarsland's insights into biomarker use took delegates on a journey from pathology to the practical impact and outcomes for the patients, and Dr Paul Donaghy's session on prodromal DLB were both well received, whilst the lightning talks from an expert panel injected the room with energy and enthusiasm. Later, that same panel discussed five different cases depicting diagnostic challenges and management, inviting open discussion from delegates and enabling peer-to-peer support and experience-sharing.

Education should always impact practice, and 95% of delegate evaluations said that the content would significantly or highly influence them in making modifications to their practice. Eight delegates specifically announced their intention to utilise the DIAMOND Lewy toolkit [4] in their clinical practice after hearing Prof John O'Brien speak eloquently on the importance of appropriate assessment, and of building opportunities for detection into core clinical practice.

One delegate noted:

> 'The DIAMOND Lewy toolkit [5]] improves core knowledge for the family and patient. Then, it is not such a shock when the patient starts to display unusual behaviour. I think using [the toolkit] would lead to less admissions.

People affected by Lewy body dementia themselves are experts on the condition in a very different and equally essential way, and midway in the programme a panel of individuals with lived experience of LBD shared their expertise. Led by Rachel Thompson, the panel considered the importance of care pathway planning for Lewy body dementia, from diagnosis through to the end of life, with each speaker sharing their own experiences.

One delegate remarked:

> 'It was a privilege to hear these four individuals speaking today. Fantastic to have insight into patient and carers' views and how they have experienced diagnosis, etc. This will have an impact on how I approach clinics as a trainee in Old Age Psychiatry.'

The course was rounded off by Karen Meenan, Jacqui Cannon and Helen Bundy Medsger from the Lewy Body Society and the Lewy Body Dementia Association respectively, who provided an informative session highlighting the value of the voluntary sector and the community support available for families affected by Lewy body dementia.

Future plans

With speakers and delegates alike feeling positive about both the content and usefulness of this course, and with over 100 healthcare professionals expressing an interest in a future event, there are hopes of replicating the course in 2022.

Half of the speakers have offered to share their presentations in the future, and Lewy body Academy may offer these as preparatory material for the next MasterClass, enabling the associated in-person sessions to delve more deeply into case-based discussion and practical management.

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Annual Meeting of the American Epilepsy Society (AES) 2021

Conference details: 3-7 December, 2021, Chicago, USA. ***Report by:*** Ignacio Valencia, MD, St Christopher's Hospital for Children, USA. ***Conflict of interest statement:*** None declared.

As the first in-person meeting for American Epilepsy Society after the COVID-19 pandemic, the 2021 AES Annual Meeting brought challenges and opportunities. The 2020 Annual Meeting was run on a 100% virtual platform creating a stepping stone for this first AES hybrid meeting. With a moving target of COVID-19 numbers, the in-person meeting was carefully planned to adhere to the latest CDC guidelines, while the Digital Select offering provided access to a substantial portion of the educational content for those unable to travel. This 75th AES meeting was able to safely bring together almost 4,000 people in-person and over 1,700 virtually.

The largest convention centre in the US, the McCormick Place Convention Center in Chicago was the perfect setting for allowing social distancing and plenty of space for safe learning and socialising. The AES Annual Meeting gathers professionals from multiple fields with one focus: Epilepsy. Through dissemination of research and education AES aims to improve the quality of life of people with epilepsy. AES includes the entire epilepsy community in the planning and delivery of its educational sessions and has increased its focus on addressing healthcare disparities through its educational programmes. This was clear throughout the 2021 meeting and was very well received.

As usual, the 2021 AES meeting was arranged over five days, with multiple learning opportunities for different learning styles and levels of expertise. From the larger full-sized symposia to the small group discussions that allow participants good exchange of ideas the AES meeting has it all. Feedback from prior years and an assessment of knowledge gaps as well as the most current new information help the meeting to continuously improve from year to year. This year's AES offered almost 180 education hours. In addition, participants have three months after the meeting to access digital content from the meeting.

The Epilepsy Specialist Symposium opened the first day of the meeting. A neurosurgical symposium this year, this three-hour case-driven course took the audience through the different intricacies and latest technologies of epilepsy surgery. A special session was held on Sodium Channel Blocking Antiseizure Medications and the heart, addressing recent FDA warnings on this type of medication. The Annual Fundamentals Symposium discussed epilepsy therapies in different patient populations while the ILAE North American Symposium examined the application of algorithms and artificial intelligence in epilepsy care. The special Judith Hoyer lecture was given this year by President Emeritus Dr Page Pennell, on contemporary care for women with epilepsy. This first day was wrapped-up by the Spanish Symposium, and the small group Basic Science Skills, Investigator workshops and special interest groups.

The main course of the second day of the meeting was the Presidential Symposium, Pediatric State of the Art, and Best Practices in Clinical Epilepsy. These dealt respectively with recent research revolutions, electrical status epilepticus in sleep and complexity of care across the age spectrum. This was also the first of three days where over 1,300 researchers from around the world presented their posters or platforms and engaged in discussion of their latest investigations. They had the chance to do this virtually or in person.

The Annual Course and Merritt-Putnam Symposium were highlights of the third day. The Annual Course was a full day event detailing how to help patients live with epilepsy. This important event addressed issues including access to care, resources outside of the epilepsy office, and the future of epilepsy care. DJ Hapa, an internationally known disc jockey and an advocate for epilepsy, made brief introductions during the day of his own story, bringing a very special personal touch to this symposium. The Merritt-Putnam Symposium focused on recent genetic discoveries and how these have led to precision medicine application for specific epilepsy therapies.

Three main symposia were held on the fourth day of the meeting: Advanced Practice Provider, Hot Topics, and Scientific. The Advanced Practice Provider Symposium brought professionals from different fields to speak on sensitive topics including SUDEP (Sudden Unexpected Death in Epilepsy), gender issues, and epilepsy during pregnancy. A special lecture and the Hot Topics Symposium updated the current state of knowledge of COVID-19 and its effects on epilepsy. The Scientific Symposium was dedicated to multiscale simulations to probe mechanisms and target epilepsy treatments. The highly scientific Lombroso Lecture was the icing on the cake on the fourth day on Seizure-induced Epigenetic Regulation of Cognition in Alzheimer's Disease.

The last day of the meeting covered the Epilepsy Therapies and Translational Research symposia. The first one described the latest medical and surgical therapies for refractory generalised epilepsies, and the latter presented novel translational research examples that can serve as models for future epilepsy projects.

The 2021 AES Annual Meeting implemented a hybrid model (in-person and virtual) with multiple, big and small parallel learning and interaction opportunities. Participants can replay, review or view unseen material up to three months after the meeting. The main symposia were intertwined with a variety of smaller sessions including workshops, special interest groups, platforms and posters providing an ideal opportunity for dialogue. Live and off-line digital access during and after the meeting boosted involvement and reach for the programme allowing participants to learn at their own pace. Is this the future of scientific meetings?

BNA Festive Symposium 2021

Conference details: 13 December, 2021. Conference streamed virtually. ***Report by:*** Ivelina Dobreva, Research Assistant at the Dementia Research Centre, UCL, UK.
Conflict of interest statement: None declared.

As one of the most popular events in the neuroscience calendar, this year's BNA Festive Symposium kick-started the BNA's annual theme for 2022 – Artificial Intelligence – what can AI tell us about biological intelligence, and how can AI be used to interrogate neuroscience data and learn more about the nervous system?

The festive symposium was held online, greatly increasing accessibility and allowing people to join a day filled with neuroscience, AI, and festive fun from any part of the world.

At first glance, it is almost impossible to tie Christmas, Artificial Intelligence, and Neuroscience together and produce a themed talk! However, the fantastic speakers not only managed to tie each talk to the festive season (especially Dr Dan Jamieson who involved the audience in a journey to saving Christmas through AI) but some took it a step further and dressed up for the occasion! The whole panel team opened the symposium and welcomed the audience with wonderful Santa hats and Christmas jumpers which set the mood for the whole day of festive science talks!

The day was split into five sessions of talks and announcements of BNA awards and prizes winners. The first session was chaired by the BNA president Prof Rik Henson and saw talks by Prof Christopher Summerfield and Dr Dan Jamieson. Prof Summerfield discussed the trajectory of developments in AI and how those can not only bring major changes in our everyday lives but also in neuroscience research. He particularly focused on how artificial intelligence invites us to consider the limitations of current neuroscience research and how we could use this to develop new research opportunities. For example, one key point raised at the beginning of his talk is the nature of neuroscience research to study parts of the brain in isolation.

Despite successful collaboration between labs scientists tend to focus their investigation of one small part of the brain, ignoring the rest. The really hard problem, Prof Summerfield argues, is figuring out how different functions are integrated, and how different brain regions communicate with each other. In fact, AI can offer solutions in this matter – whether one likes it or not, an AI agent would not work unless its individual components are pieced together. Thus, instead of focusing on how memory, or perception, or decision-making work in isolation, one would have to integrate all of these to produce an AI agent. With the advances in AI technology, such problems could offer changes in how neuroscience research is done – helping scientists embrace the notion of structured computation by understanding how whole networks work.

Then, Dr Jamieson, a CEO and co-founder of Biorelate, discussed the power of AI and deep learning to process and understand scientific articles. With the help of such processing software services, he argued, scientists can not only save time during literature searches (the software can auto-curate over 30 million articles in under six hours) but also make connections between relatively distant concepts and accelerate research intelligence. The creativity of Dr Jamieson did not go unnoticed, for his talk was framed within a Christmas fable – could Biorelate save Christmas by utilising such powerful software and finding a disease cure for his reindeers before Christmas? Spoiler alert – Christmas was saved!

The second session, again chaired by Prof Henson, saw Prof Mihaela van der Schaar discuss Quantitative Epistemology. This is a new area of research pioneered by herself and members of her lab in Cambridge as a strand of machine learning aimed at understanding, supporting, and improving human decision making. Their work includes studying and identifying suboptimalities in beliefs and decision-making processes and constructing support systems to empower better decision making.

Prof Aldo Faisal then followed with a talk on harnessing the power of AI in changing how we do science. His talk highlighted ways in which humans and machines can interact and focused on different methods of machine learning.

After a short break, in a session chaired by Prof Tara Spires-Jones, Dr Sadhana Sharma discussed upcoming funding opportunities at the interface of AI and neuroscience and Prof Thomas Nowotny spoke about utilisations of algorithms inspired by insect anatomy. Prof Nowotny made a very interesting case of using less-sophisticated, insect-inspired algorithms as the basis of more robust and efficient AI.

In the last talks of the day, Prof Eleni Vasilaki discussed sparse reservoir computing – an approach of introducing sparsity into a reservoir computing network making neurons with low thresholds contribute to decision making whilst suppressing information from neurons with high thresholds. This approach, which her team term "SpaRCe", optimises the sparsity level of the reservoir without affecting the reservoir dynamics. With such approach, SpaRCe alleviates the problem of catastrophic forgetting.

Dr George Cevora-Arca Blanca then spoke about instability in AI, portrayed through adversarial examples – a tiny, but carefully designed change to a picture, which would be imperceptible to humans, causes a machine vision to dramatically change its classification of the image. This may pose a significant danger when AI systems are deployed and misled – for example a self-driving car could mis-recognise a STOP sign on a road, with potentially catastrophic consequences. In his talk, George argued that instability may be unavoidable in light of how we currently frame Machine Vision tasks, but solutions do exist to make AI systems safe. Additionally, he postulated that humans are not immune to adversarial examples, but their occurrence is extremely improbable.

Finally, Dr Henry Shelvin discussed the advances of language processing capabilities of AI and gave us a few examples of AI 'friends' such as Replika and Woebot. Many users seem to attribute sincere thoughts, desires, and even emotions to the systems they interact with, forming sometimes deep relationships. Yet, what is the value of human-robot friendship? Cognitive scientists largely do not take the attribution of mental states to these systems seriously. This creates a dilemma for cognitive scientists in the upcoming decades: should they play the role of 'killjoys' and attempt to debunk the idea that these systems have mental states, or – in light of changing norms of ascription among the general public – instead attempt to revise their scientific concepts to accommodate these 'uncanny communicators'? To end with a quote from his talk: "Deciding where to draw the mental line between machines and beings with minds is going to prove a contentious question for all of us to tackle together."

In between these talks, BNA 2021 awards for undergraduate, postgraduate as well as the prestigious award for Outstanding Contribution to Neuroscience and Public Engagement of Neuroscience were announced. You can follow this link to find more about the winners: https://www.bna.org.uk/mediacentre/news/bna-prize/

FEATURED EVENTS

ILAE British Branch 18th Specialist Registrar Epilepsy Teaching Weekend
Saturday 14 - Sunday 15 May 2022;
Teaching and Learning Centre at Birmingham University, Birmingham, UK.
www.epilepsyteachingweekend.com

ILAE British Branch Annual Scientific Meeting
Wednesday 12 October - Friday 14 October 2022
City Hall, Cardiff, Wales.
www.ilaebritishconference.org.uk

For more upcoming events please visit our website – www.acnr.co.uk/event
These dates are correct as we go to press. Please check with the organisers for any changes due to the COVID-19 pandemic. Please send diary listings for our website and next issue to Rachael@acnr.co.uk