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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

CLINICAL REVIEW ARTICLES > BOOK REVIEWS > CONFERENCE REPORTS > SPECIAL FEATURES

CONTENTS

VOLUME 22 ISSUE 1

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FROM THE CO-EDITOR...

I'm writing this at a time of uncertainty in the United Kingdom, with potential strikes and the 'Beast from the East' coming towards us. Of course we are not only read in the UK, which is reflected in the scope of our editorial board, and we welcome a review of CGRP receptor antibodies from Professor Uwe Reuter, from Charité University Hospital of Berlin as part of our headache series.

In this issue we welcome our first article in a series commissioned by our stroke editor Dr Martin Punter, Wellington, New Zealand, looking at the hyperacute management of intracranial haemorrhage, authored by Alastair Paterson and Dr Adrian Parry Jones.

As part of our continuing series from the Centre for Neurorehabilitation at UCLH, London, Ben Beare looks at what we know about post stroke shoulder pain, and the options for treatment of this common and debilitating symptom.

Neuropsychologist Dr Phil Moore looks at the evidence for using EDMR (eye movement desensitisation reprocessing) therapy to potentially help patients who experience distressing 'islands of memory' while they are recovering from traumatic brain injury.

Looking back at neurologists of old, there is a fascinating article once again from JMS Pearce, about Franciscus Sylvius - a neuroanatomist par excellence, who named a fissure and an aqueduct, and may also, if I understand correctly, have been an early discoverer of gin. We have much to thank him for.

Closer chronologically and geographically, Professor David Marsden is a name familiar to every London trainee for generations and acclaimed worldwide, for his achievements in movement disorder research. Dr AJ Larner looks at his less well known achievements in the field of cognitive neurology.

On the movement disorder theme Dr Tom Gilberston (Dundee) and Mr Sadaquate Khan (Edinburgh) provide us with an in depth update on MR guided focused ultrasound for tremor.

Elsewhere there is a review by Sharon Witton (OT, Leeds) of the Fatigue book, by Lydia Rolley and Dr Pawel Obrocki (Neurology SpR, Royal Free London) updates us on the latest version of Aids to the Examination of the Peripheral Nervous System by Dr Michael O'Brien on behalf of the guarantors of Brain.

Conference reviews include the triMSx Webinar- Smouldering MS what is it? (Chaired by Professor Gavin Giovannoni who kindly provided the report), Encephalitis Conference 2022 (report Dr Ava Easton), British Society of Physical and Rehabilitation Medicine (BSPRM), with the president elect Dr Manoj Sivan (report by Asma Khan).

So all in all, a packed issue, and our gratitude goes to all of our contributors and section editors.

Ann Donnelly, Co-Editor
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Dr Maria Spir Brunal Wins WFNR Franz Gerstenbrand Award

Dr Maria Alejandra Spir Brunal, medical researcher at the University of Antioquia, Medellin, Colombia, has been presented with the 2022 WFNR Franz Gerstenbrand Award.

Maria's research has resulted in the development of educational resources for individuals who have moderate to severe brain injury, their families, and caregivers. The resources include a mobile phone application, an educational book and videos to explain the different phases and changes that individuals with brain injury experience as in-patients, during the rehabilitation process and also in their day-to-day lives.

The mobile application uses graphics, videos and interactive sessions and makes recommendations for in-patients, home care, long-term care and for the care of some specific conditions associated with TBI. The app is available at: https://apps.apple.com/co/app/cuidatec/id1639039499

Dr Maria Spir Brunal receives the WFNR Franz Gerstenbrand Award from Professor David Good (now WFNR Past-President) at the 12th World Congress for Neurorehabilitation, December 2022, Vienna, Austria.

Gabriele Lignani Awarded 2023 Michael Prize

Congratulations to Dr Gabriele Lignani, who has been awarded the 2023 Michael Prize. The Michael Prize is one of the most highly regarded international awards for the best scientific contribution to progress in the field of epileptology. Dr Gabriele Lignani (Associate Professor, Clinical & Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK) was awarded the prize in the field of experimental epilepsy research. He will receive the prize at the 35th International Epilepsy Congress, 2-6 September 2023.

UCL

Queen Square Multidisciplinary Neuro-oncology Teaching Course

Location: 33 Queen Square lecture theatre Course Director: Dr Jeremy Rees

27th September 2023: Principles of Neuro-oncology & 6th March 2023:Benign and Malignant Tumours

The need for multidisciplinary working in Neuro-oncology is well established but a common theme that will be addressed is the need for better understanding between core specialties within the Neuro-oncology Multidisciplinary Team. To address this, this course has been designed for Trainees, Consultants and Clinical Nurse Specialists in the core specialities of neuro-oncology – Neurology, Neurosurgery, Clinical Oncology, Neuroradiology, Neuropathology and Palliative Care.

Course fees:

Category	Full course rate	Day rate
Consultants	140	100
Trainees	90	70
Students	15	10
UCLH Staff	0	0
Allied professionals (physios, nurses etc)	70	50

www.ucl.ac.uk/ion/queen-square-multidisciplinary-neuro-oncology-teaching-course

The 4th Queen Square Movement Disorders Short Course

12th-13th October 2023, 33 Queen Square Lecture Theatre, London, UK Course Organisers: Prof Anthony Schapira and Dr Amit Batla

On completion, participants should be able to manage patients with movement disorders in their clinical practice with updated knowledge and confidence. The teaching sessions cover all aspects of movement disorders including Parkinson's disease and atypical parkinsonism, tremor, dystonia, tics and functional movement disorders. Presentations on Deep Brain stimulation and Botulinum toxin injections.

The course is endorsed by International Parkinson and Movement Disorder Society (MDS). The Queen Square Movement Disorders Short Course has applied for CPD credit points from the Federation of the Royal Colleges of Physicians of the United Kingdom.

Course fees:

Consultant & Associate Specialists	£350.00
PhD Clinical Trainees & Research Fellows	£200.00
UCL Medical Students, BSc, MSc students	£100.00
Nursing Staff, therapists, paramedics (NHS)	£100.00
Day registration (one day only)	£200.00

Linda Taib: l.taib@ucl.ac.uk

Queen Square Multiple Sclerosis (MS) Course

Queen Square MS Centre – Clinical Update
Course: 2nd and 3rd November 2023, 33 Queen Square lecture theatre, London [plus online observer registration option]
Course Directors: Professor Ahmed Toosy and Dr Declan Chard

Covers key clinical issues in MS, serving as an update on this advancing field. Accessible to non-neurologists and neurologists. Lecturers have all been chosen for expertise and relevant experience in clinical practice and research.

10 CPD approved credits applied for.

www.ucl.ac.uk/ion/study/virtual-queen-square-multiple-sclerosis-ms-course-clinical-update **Info: h.ormsby@ucl.ac.uk**

Monoclonal CGRP-(R) antibodies for the prevention of migraine

Uwe Reuter, MD, PhD, MBA, is a Professor of Neurology at Charité University Hospital of Berlin and Chief Medical Officer at Universitätsmedizin Greifswald. He is a graduate of Johannes Gutenberg-Universität Mainz. He completed three years of postdoctoral studies at Harvard Medical School. At Harvard, Uwe focused on basic research in primary headaches and migraine aura. He continues his clinical practice and research in basic and clinical headaches. He is a member of several national and international headache organisations, and currently serves as board member of the European Headache Federation.

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Provenance and peer review: Submitted and externally reviewed.

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https://doi.org/10.47795/VKEJ7377

Abstract

A new era in migraine prophylaxis has begun with the launch of antibodies blocking the Calcitonin-Gene Related Peptide (CGRP) pathway. These substances act across the entire frequency spectrum of migraine and have a tolerability superior to any other class of oral migraine preventatives based on our clinical and experimental knowledge of a 5- year period of use. Their superior tolerability profile may be due to their specificity. New questions have also arrived with these drugs ranging from the duration of therapy and treatment pause to the question of which monoclonal antibodies (mAb) for which patient - a question which we cannot answer at this stage. Nevertheless, CGRP – (R) mAbs offer a class of migraine prophylactics with significant advantages over older medications.

Migraine is a complex disorder of the central nervous system (CNS) that affects up to 15% of the adult population with a predominance in females. While the vast majority of individuals with migraine suffer from very low frequency episodic migraine (<4 monthly migraine days (MMD) /month), a significant minority that are severely affected by the disorder require pharmacological migraine prevention (<20%). These are in general individuals with chronic migraine or high frequency episodic migraine with at least 8 MMD. In subjects with low frequency episodic migraine prophylaxis can also be necessary depending on the success of single attack therapy.

The pharmaceutical treatment armentarium of prophylactics consists of oral preventatives such as topiramate, beta blockers, tricyclics and others, which were developed for other diseases and made their way into migraine by chance. Onabotulinum toxin (i.m.) is only licensed for the prevention of chronic migraine.

Drugs targeting Calcitonin gene related peptide (CGRP) or the CGRP-receptor (R) were introduced in Europe in autumn 2018. They form the only class of substances specifically designed for the prevention of migraine. All four CGRP-(R) mAbs are approved for the prevention of migraine in patients with at least 4 MMD, which includes patients with episodic and chronic migraine. Chronic migraine is defined as a headache disorder with at least 15 headache days /month of which at least 8 need to have migrainous features (for more than 3 months). Numerous analyses indicated that these drugs have significantly better tolerability than older medications [1].

Characteristics of CGRP- (R) mAbs

The first Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved CGRP antibody was erenumab, which is the only one that binds and blocks the CGRP receptor. Subsequently the antibodies blocking CGRP named galcanezumab, fremanezumab and most recently eptinezumab became available. While the first three launched antibodies are used in a s.c. formulation, eptinezumab is administered intravenously. These substances are highly specific and seem to act outside the CNS at the level of the trigeminal ganglion and/or at the node of Ranvier of primary afferent trigeminal neurons.

Possible actions may also include mast cells and meningeal arteries. Due to their molecular size, they do not penetrate the blood brain barrier in relevant amounts. CGRP-(R) mAbs are metabolised by the reticular endothelial system and are thereby devoid of liver or kidney toxicity. Typically, they do not interact with other medications. CGRP and the CGRP receptor exists in numerous tissues throughout the body.

Since CGRP and the CGRP-(R) are involved in arterial vasodilation, a potential risk of deterioration of vascular disease such as angina, myocardial infarction or stroke with the use of these mAbs was suspected prior to clinical use. These adverse events have fortunately not been described in real world studies with a clear causal relationship to the use of CGRP blocking agents. Of note one case of stroke has been described with a temporal relationship to a mAb injection [2].

A treadmill trial in males with severe cardiovascular disease, who were exposed to IV erenumab or a placebo did not show any different results between both groups, indicating that redundant mechanisms for vasodilation may exist. Whether the results of this trial in males reflect conditions in women with predominantly small vessel artery disease is a matter of debate. However, the FDA has issued a warning from post-marketing surveillance that blocking the CGRP receptor with erenumab may lead to an increased risk of hypertension or the deterioration of existing hypertension. Also, constipation has been described as a side effect of erenumab and to a smaller degree with CGRP ligand mAbs. According to clinical trials and real-world observations, constipation is typically mild and does not usually lead to treatment termination.

Other adverse events of CGRP-(R) mAbs include anaphylaxis (more pronounced when using an IV formulation), allergic reactions or local pain and swelling after injection. The

worsening or development of Raynaud´s syndrome has also been described. Of note, in a mouse model of transient ischaemia two small molecule CGRP receptor antagonists led to increased infarct size due to reduced blood flow [3].

Efficacy of CGRP- (R) mAbs

In the meantime, real world studies have confirmed efficacy and tolerability data from Phase II and III placebo-controlled randomised, double-blind clinical trials (Figure 1). In fact, the efficacy of erenumab, galcanezumab and fremanezumab exceeds data from clinical trials especially in the most severely affected patient populations with frequent migraine days and numerous prior preventive unsuccessful therapies. Several groups across the globe reported convincing efficacy data in different ethnic populations.

The most severely affected patients have not been studied in placebo controlled, randomised, double-blind clinical trials. Only patients with up to four unsuccessful preventive therapies have been studied in this design (see Table 1). The first of this series of studies in episodic migraine (EM) (LIBERTY; 9.4 MMDs at baseline) with a monthly dose of erenumab s.c. 140 mg, or placebo showed that 30% of patients on erenumab reach at least a 50% reduction of MMD in the third treatment month [4].

Subsequent trials with fremanezumab and galcanezumab confirmed these findings and expanded upon the chronic migraine spectrum [5,6]. Most recently the intravenous formulation of eptinezumab completed this successful series of studies [7]. In general, the secondary endpoints were also reached in these studies. These include the reduction of acute medication use or the improvement of quality of life or total migraine burden in the CONQUER study with galcanezumab [6]. All four studies revealed that the number of prior non-successful therapies does not predict the success of CGRP- (R) mAb prophylactic therapy.

Long term follow up of the LIBERTY trial showed a consistency of efficacy up to 3 years with monthly erenumab 140mg with a 50% reduction in MMD in more than 50% of study participants. The high retention rate (>70%) of participants in the trial over three years especially indicates a beneficial tolerability and efficacy profile of erenumab. Three-year data of the CGRP antibodies in this more difficult population of individuals with migraine have not been reported. However, one-year data exist and indicate consistency of efficacy and no new adverse events.

Prior to these clinical trials, all CGRP-(R) were studied in patients with episodic and chronic migraine with up to two and three, respectively, previous preventive treatment failures, a population typically seen by headache specialists. Needless to say, all four substances passed these trials successfully. For example, the STRIVE study showed the efficacy of erenumab 70 mg and 140 mg in a six-month trial versus placebo [8]. In the galcanezumab clinical trials the loading dose of 240 mg followed by monthly doses of 120 mg were identified as the ideal treatment scheme in EM and CM for this substance based on efficacy and tolerability [9]. The EM trial by Dodick et al., showed that the efficacy of quarterly doses of fremanezumab (675 mg s.c.) is in the range of the monthly dosing scheme (225 mg s.c.) without additional side effects [10].

Table 1: Results from CGRP-(R) mAbs in placebo controlled, randomised, double blind trials in patients with 2-4 non successful therapies.

Substance YoP*	Erenumab (2018)	Fremanezumab (2019)	Galcanezumab (2021)	Eptinezumab (2022)
	LIBERTY NCT03096834	FOCUS NCT03308968	CONQER NCT03559257	DELIVER NCT04418765
Population	EM	EM/CM	EM/CM	EM/CM
Dosage	140 mg/pl	225mg/675mg/pl	120mg/pl	100mg/300mg/pl
n	121/125	283/276/279	232/230	299/294/298
Baseline MMD	9,2/9,3	14,1/14,1/14,3	13,4/13,0	13,8/13,7/13,9
Primary endpoint	50% RR in weeks 8-12 of the DB period	Change From Baseline in Monthly Average Number of Migraine Days During the 12-Week DB period	Mean Change from Baseline in the Number of Monthly Migraine Headache Days [Baseline, Month 3]	Change from Baseline in the Number of Monthly Migraine Days (w 1-12)
	30,3%/13,7%	-4,1/-3,7/-0,6	-4,1/-1	-4,8 /-5,3 /-2,1
SAEs	1,6/0,8%	3,8%/3,6%/4,2%	1%/1%	2%/2%/1%
Adverse events	37/34	28/32/31	9/13	42/41/40

* YoP: Year of publication; pl: placebo

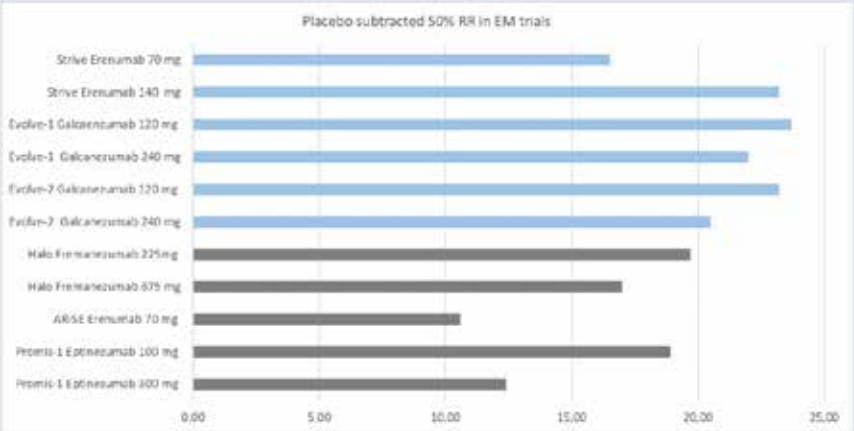

Figure 1: Placebo subtracted 50% Responder rates in placebo controlled, randomized, double-blind EM trials; blue bars indicate a trial duration of 6 month; grey bars indicate a trial duration of 3 months.

The PROMISE trials identified the 100 mg and 300mg eptinezumab IV dose as the ideal dosing scheme for this substance [11]. In all of these studies active drugs also led to a greater improvement of headache related quality of life than the placebo. It is important to note that all substances resulted in the improvement in several of the following fields: reduction of specific/unspecific acute migraine medication, work and productivity, total migraine burden and migraine related disability. All four mAbs have also demonstrated efficacy in the chronic migraine patient population [12]. Unfortunately, these trials consisted of only a three month double blind treatment phase, which is too short to explore the full efficacy of active drugs vs placebo in this patient population. However, long term open label study data in CM patients exist up to one year [13]. Most certainly the efficacy is sustained for a period of at least one year. Based on these open label trials it appears that the efficacy of CGRP-(R) mAbs increases over time in the CM population, but the lack of a placebo group does not allow us to make such statement with certainty.

In several European countries CGRP-(R) mAb therapy for migraine prophylaxis must be stopped after 9-12 months of successful therapy in order to evaluate disease modifying effects i.e. the ongoing reduction of MMDs in a drug free interval. Most recently published real world data from Italy, Switzerland and Germany showed that MMD increase from months 2 onwards after treatment termination [14]. In

the 3rd month of medication pause, MMDs in most patients are close to the baseline levels before CGRP mAb initiation. In line, the quality of life deteriorates significantly during the drug holiday as assessed by HIT-6, EuroQol-5-Dimension-5-Level (ED-5D-5L) form and the Short-Form 12 (SF-12). These findings indicate that CGRP mAbs have no disease modifying effects. Raffaelli et al showed in a small sample (n=39) that 72,8% of patients responded after resumption of therapy to the same CGRP mAb they had before the medication pause [15]. Although controlled randomised studies are missing the implementation of a forced medication pause in patients successfully treated with a CGRP mAb is of limited use.

The CGRP mAbs are safe molecules in the prophylaxis of migraine with good tolerability. Recently 5-year data has been published for erenumab. In this cohort the efficacy was sustained during the entire trial period and no new adverse events were discovered [17]. In most European countries CGRP – (R) mAbs are not first line therapies for the prevention of migraine, mainly due to country specific economic reasons. However, looking at the data and comparing the CGRP- (R) mAbs to oral migraine prophylactics there is little rationale behind such a decision on scientific grounds. In fact, erenumab was studied versus topiramate in a randomised double-blind, double dummy trial in migraine prophylaxis in 777 patients with 10.4 MMDs at baseline. As expected, erenumab had a better tolerability in this trial than topiramate. However, the effectiveness of therapy was also significantly better in the erenumab group than the topiramate group [15]. Also, in study completers erenumab was more efficacious than a daily dose of 92 mg of topiramate.

In summary, CGRP mAbs offer a class of effective and tolerable migraine preventive medications, which should be considered as therapy by physicians at all times of a patient's migraine journey.

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Beneficial effects of median nerve stimulation on Tourette syndrome

Results of UK-wide double-blind sham-controlled clinical trial of the Neupulse device for suppressing tics in Tourette syndrome

The trial was run by the University of Nottingham, conducted between 18th March 2022 and 5th of March 2023, sponsored by Nottingham University Hospitals NHS Trust. The aim was to evaluate the effectiveness of the Neupulse device in reducing the severity and frequency of tics in individuals with Tourette Syndrome. A total of 121 participants took part in the study and went on to receive either active or sham stimulation for 10 minutes a day for four weeks.

The results of the study revealed that people who received active stimulation experienced a significant reduction in the severity and frequency of their tics. On average, they saw a reduction in tic frequency of more than 25% while they received stimulation.

After using the device for 4 weeks, people who received active stimulation experienced a reduction in their tic severity of more than 35%. In total, 59% of the people who received active stimulation experienced a reduction in tic severity of at least 25% compared to baseline.

These positive results will help start the development of a commercial medical device, that will run for the next 18 months. Neupulse hope to obtain regulatory approval for a commercial device by 2025 and have a device available by 2026.

Treating distressing islands of memory: severe TBI and EMDR treatment for distressing experiences during post traumatic amnesia

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is a Consultant Neuropsychologist & Clinical Psychologist and Director of Medicolegal-Psychology-Neuropsychology Ltd. He has a special interest in expert witness neuropsychological assessment of traumatic brain injury and case funded neuropsychological treatment of traumatic brain injury and psychological trauma.
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Conflict of Interest Statement: None declared

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Submitted and reviewed internally.

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Acceptance Date: 15/12/2022

Ethics Statement: Ethics approval was not needed for this case report. The patient described here gave an informed consent for the publication of her clinical details and comments.

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https://doi.org/10.47795/UTTR3399

Abstract
'Severe' Traumatic Brain Injury (TBI) survivors are likely to be hospitalised and experience Post Traumatic Amnesia (PTA): a transient state of confusion, disorientation and memory loss, until the return of continuous memory. Survivors often experience distressing 'islands' of memory during PTA, and this can exacerbate psychological deterioration and lead to additional poor outcomes if left untreated. The literature for neuropsychological rehabilitation is well established in the multidisciplinary delivery of services for severe TBI, but the alleviation of post-traumatic distress caused during PTA has received little attention to date. This case report demonstrates how Eye Movement Desensitisation Reprocessing (EMDR) therapy might provide psychological improvement in clients who sustain severe TBI with distressing 'islands' of memory during PTA and provides a 4 year follow up to measure sustained benefits.

Survivors of severe TBI have by definition experienced a near death event. Consensus has moved on from earlier opinions that severe TBI was mutually exclusive with post-traumatic stress disorder (PTSD) due to loss of consciousness, with evidence that approximately 27% of severe TBI patients meet the full clinical criteria for PTSD at 6 months post injury [1] and signs of elevations in stress hormone exist at one week for those who do go on to develop PTSD [1].

Severe TBI survivors will often have a prolonged stay in ICU experiencing confusion, delirium, mechanical ventilation, restrictive care practices, sedation, injury pain, intrusive medical procedures and a growing realisation of potential mortality, and 'islands' of memory. 'Islands of memory' can often be distressing presenting challenges to optimal recovery during neurorehabilitation, including poorer psychosocial outcomes [2].

Neuropsychological treatment typically involves aspects of psychoeducation, cognitive rehabilitation, the implementation of strategies to compensate for cognitive problems and, where appropriate, brief psychological therapy interventions for associated psychological difficulties. Eye Movement De-Sensitisation Reprocessing (EMDR) is based on the idea that negative thoughts, feelings and behaviours are the result of unprocessed memories. The treatment involves procedures that include focusing simultaneously on spontaneous associations of traumatic images, thoughts, emotions and bodily sensations and bilateral stimulation (bilateral eye stimulation predominantly). EMDR evidence in brain injury is scarce with some recent attention in alleviating emotional symptoms in cases of mild TBI [3], although its use is growing.

Case Study

'Maria' was a UK born female in her 50s. She sustained a severe traumatic brain injury causing unconsciousness, skull fracture, right frontotemporal extradural haematoma, left posterior temporal contusions, subarachnoid haemorrhage and a last recorded GCS of 3 before sedation and induced coma for 8 days. Maria's intracranial pressure was monitored via a bolt, but no neurosurgery was elected. She experienced PTA for 3 weeks. She had no clear recall of events on the day of the index event. She also received severe orthopaedic injuries to the neck, back and ribs, and it was deemed that her chances of survival were relatively low. She was in intensive care for 11 days, and under hospital care for approximately 4 weeks. She received community based NHS neurorehabilitation and thereafter at 9 weeks post injury, received private multidisciplinary neuro-rehabilitation through the litigation process.

An initial home visit assessment was provided for Maria at her family home.

Table 1. Repeatable Battery for Neuropsychological Status (UK norms)

Scale	Index Score	Percentile
Immediate memory	117	87th
Visuospatial/constructional	126	96th
Language	131	98th
Attention	125	95th
Delayed memory	119	90th
Total	141	99.7th

On first meeting her presentation was non-remarkable other than occasional high-level word finding difficulties, and slightly flattened mood. Physical pain from her injuries was still evident. Maria was highly educated and appeared motivated to recover as far as possible. At the time of initial neuropsychological assessment she had returned to work on a part-time basis with reasonable adjustments to include increased breaks and reduced management responsibilities. She had no significant psychological or neurological history and was in good health before the brain injury. Maria was asked, from her perspective, what has been the impact of her brain injury. She replied:

"I'm frustrated by my slowness and inefficiency at work…. I become frustrated at times and although my colleagues have been supportive I probably put pressure on myself. I tried to get back to normal as soon as possible. I haven't cried since the injury... I sometimes feel that people have to spell out their intentions as I find it more difficult to pick up on social nuances. I'm not as good at remembering new things. Memories fade quicker from my awareness and I have to write more down now since the accident."

Her cognition during initial neuropsychological assessment was assessed using the Repeatable Battery for Neuropsychological status - UK (RBANS-UK). Results mirrored expectations of high intellect with an overall index score of 141, putting Maria in the top 99.7% compared to UK based cognitively healthy age-related peers. Maria's performance on standardised memory tasks and information processing cognitive tasks was weakest in comparison to her other domain scores, but still considerably above 'average'. These results were consistent with Maria's perceived cognitive changes. She passed embedded measures of performance validity (reliable digit span).

Following neuropsychological assessment, Maria received feedback on her results and two psycho-education sessions on brain injury. No further cognitive assessments were undertaken as it became clear that Maria had more prominent emotional based therapeutic needs. She reported:

"The impact upon children who I teach was distressing. Reading the cards of well wishers was very hard. I found it hard to process others emotions… before realising the impact upon myself."

Maria soon explained that she had become distressed from her experiences particularly her survival and recovery within acute medical care and PTA especially. She was assessed for symptoms of psychological trauma at the start of the subsequent session and was found to have significant residual post-traumatic stress. A discussion with Maria and the treating team was undertaken it was agreed that neuropsychological treatment efforts would prioritise the treatment of her post-traumatic distress using Eye Movement Desensitisation Re-Processing Therapy (EMDR).

She completed EMDR based measures at start of treatment, at mid-point review, on final treatment (after 8 EMDR sessions) and at 4 years long term follow up. Nine 1.5 hour EMDR sessions, across a 6 month period were undertaken. The first EMDR treatment session provided EMDR focused baseline measures. Maria scored significantly on Impact of Events Scale - Revised (IES-R) at start of EMDR treatment, indicating severe symptoms of intrusive memories, avoidance behaviours and physiological hyper-arousal and surpassing cut-offs for PTSD (see Table 2). At this initial point, prior to treatment she also rated her psychologically traumatic memories associated with the accident and her recovery as significantly distressing (see Table 2).

During the first session EMDR treatment protocol moved on to orientate Maria to the therapeutic model explaining the Adaptive Information Processing (AIP) model (see [4] for more information). For Maria this made sense and she reported a clear fit with her experiences in acute care during PTA. Safe place practices were developed. History taking was conducted to establish the key distressing memories which she had held on to and was distressed most by. For Maria there were several key memories, which all revolved around feeling helpless and in pain. She explained her most distressing memory to be:

"The key distressing memory was waking up - my first awareness of being in ICU. I recall the breathing tube being removed from my throat. It was painful and I am not sure if I was trying to pull it out, or if it was being removed. I didn't know where I was or who was there. It felt like a nightmare, without the chance to realise it wasn't real."

Maria engaged well with the model and chose her negative cognition (NC) connected to her distressing memories, as: "I am vulnerable" and developed the positive cognition (PC): "I can cope with this. I am capable." She identified and activated the most distressing memory on the second session. Desensitisation required few cognitive interweaves (verbal prompts to elicit constructive progress). She was a very psychologically minded intellectual, who appeared to develop insight toward her psychological experience of the injury across the course of treatment. As the sessions progressed with successful 'subjective units of distress' 0-10 (SUD) reductions on each memory targeted, in turn, her validity of cognition' 1-7 VOC strengthened. Midway through treatment she reported:

"I have experienced a loss of identity and became a person I didn't recognise… The physical injuries aside - I felt I had become a person who wasn't me. I had felt like someone who needed support, in contrast to the independent person I had become across my life."

As the main distressing memory (channel) was successfully reprocessed, additional distressing memories were targeted. Her 'islands of memory' during PTA were chosen by her.

"In the times during PTA, when I saw myself I didn't recognise myself. It felt like I had woken up in someone else's body. I felt like I didn't understand why I was there. I felt at the time delusions regarding doctors having put me there. In my head it made sense that it was their fault and that made it hard to accept treatment. Everyone was concerned about the physical injuries - because they were so real, painful and visible, they took up my attention too. But there was a paranoia that the people helping me were hurting me. Every procedure which was painful

Table 2. Psychological Trauma Results

Measure	Initial Assessment	Final Treatment (8 sessions)	4 year review
IES-R	45	16	3
SUDs	8	1	3
VOCs	1	6	7

felt persecutory. I couldn't see them as helpers but part of the problem."

Maria completed her 8th EMDR session and was re-administered with all EMDR focused assessments (see results section). A planned small number of 'top-up' sessions were not completed as her litigation was settled during the following period and funding for private treatment was terminated because of this.

Results

Maria scored 45 on the IES-R at pre-EMDR treatment. This reflected severe symptoms of intrusive memories, avoidance behaviours and physiological hyperarousal, surpassing cut-offs for Post Traumatic Stress Disorder (PTSD). At this initial point, prior to treatment she also rated her 'subjective units of distress (SUDs)' associated with her PTA and acute recovery as 8 out of 10, in terms of the level of distress these memories were still causing (10 being most severe).

At the end of the 8th session midpoint her IES-R scores fell to 16, demonstrating significant reduction in intrusive memories, avoidance behaviours and physiological hyper-arousal symptoms. Her SUDs fell to 1, demonstrating significant reduction in subjective distress. Her 'validity of cognition scale' (VOC) raised from 1 to 6 out of 7, showing increased belief in her positive cognition of: "I can cope with this. I am capable". At 4 year follow-up her IES-R fell further to 3 demonstrating continued long term progress in symptom reduction. Her VOC was 7, however, her subjective distress (SUDs) increased slightly to 3.

By the time the long-term follow-up was arranged she had reflected how her way of coping had changed:

"I do talk to myself and be kinder to myself. I can rationalise things. If I find myself getting uptight about something I will talk myself through it with reassurance." When I have returned to hospital for a review it still raises feelings, but each time it has gotten easier and caused less response."

She reported her ongoing distress with the key memory as residing at 3. She described ongoing difficulties as:

"Fatigue is the main ongoing issue. I have changed things in my life so I don't feel things so badly. The fatigue gets worse through the course of the day and it is accumulative when I have a busy week. I can rest now. I still get neck and back pain and still receive physiotherapy and chiropractor treatment. I do a lot of running and yoga. I need to find time in the day to have quiet time. I have remained social but sometimes need moments of quiet and have some strategies such as popping outside or taking a deep breath."

Discussion

This case study shows promise for the application of EMDR for those who sustain severe brain injuries with associated psychological trauma during recovery. Although the wider positive effects of neurorehabilitation and neuropsychological rehabilitation cannot be neatly disentangled from the benefits of integrating EMDR, the alleviation of specific psychological trauma based symptoms was clear at end of treatment and long-term follow up in this case. Unfortunately, in this case there was very mild residual symptoms, which would likely have been addressed if treatment was not compelled to cease following litigation settlement. The further implications of this case provide support for the compatibility of EMDR for those receiving multidisciplinary neuro-rehabilitation. The case highlights the need to address psychological health following the physical focus on patient survival from severe brain injuries. The general absence of evidence for EMDR in TBI populations is baffling and warrants further empirical investigation. Single case series methodology is a good starting point, but controlled designs would test treatment efficacy compared to other treatments and hopefully better inform neuropsychological rehabilitation practice. Qualitative enquiry may also help us understand how EMDR can work for TBI clients, as Maria's comments allude to. EMDR training for Neuropsychologists provides a logical route for strengthening skills in meeting the psychological needs of TBI clients who show symptoms of psychological traumatisation. The successful integration of EMDR into multidisciplinary neurorehabilitation during litigation appears to be feasible. Long term occasional 'top-up' EMDR sessions may be required to ensure relapse prevention.

Key Points

1. Survivors of severe TBI can be psychologically traumatised post-event, especially through periods of PTA, 'islands of memory' and confusion.
2. EMDR can be integrated within wider neurorehabilitation and neuropsychologists should consider EMDR training.
3. Whilst EMDR is an evidence-based treatment for psychological trauma and stress mediated conditions, it is absent from the neuropsychological literature!

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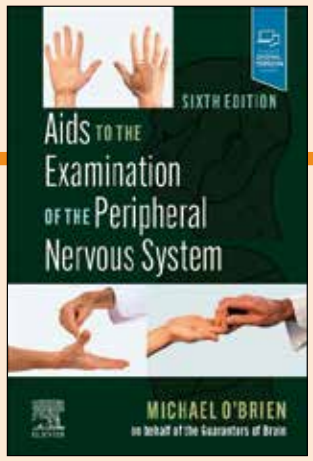
Aids to the Examination of the Peripheral Nervous System, 6th Edition



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Aids to the Examination of the peripheral nervous system was first published in 1942 in response to growing amount of peripheral nerve injuries seen by physicians and surgeons during the Second World War. Since then, it has sold thousands of copies and undergone a series of significant revisions reflecting changes to everyday neurological practice. In the process, it has become an essential component of a neurology kit for generations of trainees as well as senior neurologists.

Anyone familiar with the 5th edition of the textbook will immediately find themselves at home with the updated version as book has a near identical layout, with unchanged pictures and diagrams providing clear reference to the relevant neuroanatomy and examination techniques.

There are several changes to the 6th edition, including addition of a concise list of the most clinically relevant entrapment and compression neuropathies, which are also labelled in the relevant figures in later sections of the book. Another new addition includes a diagram of the spine and spinal nerve roots in cervical and lumbar region, as well as a new drawing of dermatomes and nerves supplying both female and male genital region. Avid readers of the textbook will also spot a new picture outlining the sensory distribution of notalgia paraesthetica and a few changes to nomenclature, with common fibular nerve now replacing the 'outdated' peroneal nerve. Lastly, for the first time the owners of the new edition will now have access to a complete digital copy of the textbook, which can be accessed and downloaded via Elsevier website to any compatible mobile device.

In the eight decades since its initial release, Aids to the Examination of the peripheral nervous system continues to improve with each edition and remains a go-to reference textbook for both specialists as well as general neurologists dealing with peripheral nerve injuries. The 6th edition is now available for purchase, with all profits from the sale of the book being donated to charity.

The Fatigue Book: Chronic Fatigue Syndrome and long COVID fatigue: practical tips for recovery

Authors: Lydia Rolley
Published by: Hammersmith Health Books
Price: £14.95
Pages: 304
ISBN: 978-1781612378
Reviewed by: Sharon Witton, Occupational Therapist, Leeds

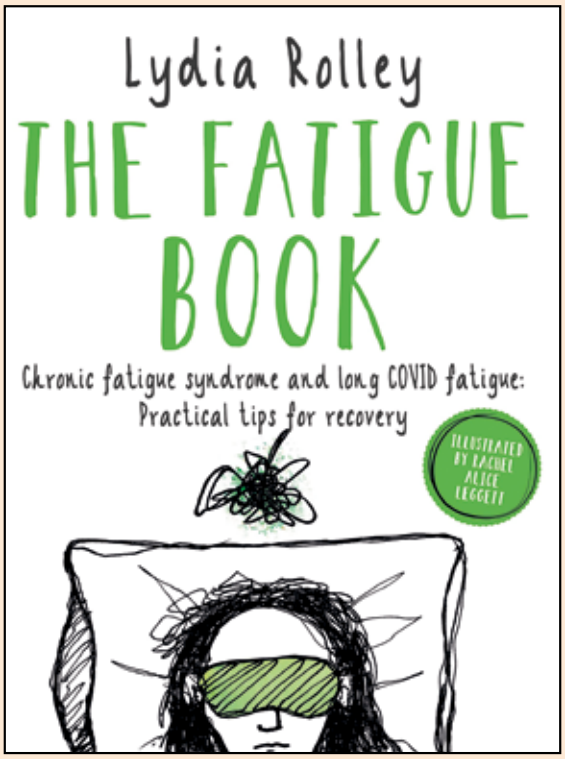
The Fatigue Book is an accessible self help book for anyone living with chronic fatigue. It may also be useful for their loved ones. There are 100 tips which are clearly defined and explained. Furthermore it is illustrated beautifully with an interesting proverb which encapsulates the complex and layered narrative.

Lydia has created a book on fatigue which concurrently validates their experience and gently informs of strategies to move towards recovery. The overriding tone of the book encapsulates the experience of a therapist who has had a long career working alongside people who are struggling with fatigue. It also shares how her faith has helped her find connection with something bigger than herself thereby addressing the spiritual fatigue which is often an ignored component in medical interventions.

Lydia's intention was to equip people with an easy to try and understand list of tools to manage fatigue. She achieves this by making the book a joyful, easy read. I would recommend it to patients who have struggled to find a way towards recovery. I would also recommend that they bought for disbelieving loved ones who would benefit from knowing all the tried and tested fatigue management interventions that have worked for others.

The references to Covid and Long Covid are mostly applicable. However they do not fully address the emerging evidence regarding post exertional symptom exacerbation and dysautonomia.

Long Covid recovery information is still emerging. However the importance of rehabilitation; which includes learning how to rest as much as how to move forward is a crucial component of recovery. Reducing crashes and finding balance between rest and activity being the most successful strategy seen amongst patients. A book including these themes of similar design and content would certainly be a further addition to the growing number of self-help books on the subject.



Understanding frozen shoulder in the hemiparetic arm after stroke

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Abstract

Frozen shoulder is more common in the weakened hemiparetic shoulder post-stroke than in the general population. Increasing age, micro-vascular co-morbidities and the presence of subluxation make the soft tissue of the hemiparetic shoulder more susceptible to injury and inflammation. Inflammation can trigger fibrosis of the shoulder ligamentous capsule due to a disruption of joint homeostasis. It is this fibrosis that results in the common presenting features of frozen shoulder, namely restriction of passive shoulder external rotation, abduction and internal rotation.

Frozen shoulder is still largely a clinical diagnosis after assessment and exclusion of other possibilities. Spasticity of shoulder adductors and internal rotators is also common in hemiparesis and is hard to differentiate from frozen shoulder. Pectoralis Major is a common contributor to adductor and internal rotator tone and so diagnostic lateral pectoralis nerve blocks (DNBs) may help to establish if this is main cause of restriction. However, several muscles often contribute to shoulder adductor and internal rotator spasticity, so there is a risk of misinterpretation of DNB results.

In cases of frozen shoulder, daily movements of the shoulder joint within tolerable pain limits can help to restore joint homeostasis and reduce pain. Steroid injection (either alone or as part of a hydrodilatation injection) when inflammation is present can also reduce pain and improve range when used in combination with physiotherapy.

Background

Post-stroke shoulder pain (PSSP) is an umbrella term that includes all forms of pain that is perceived in the hemiparetic (weakened) shoulder and upper arm post-stroke [3,30]. It can affect around 50% of those with moderate weakness and around 80% of those with severe weakness[1]. PSSP should be detected and managed as soon as possible to reduce pain and avoid disengagement with early rehabilitation that can have a devastating impact on long term outcomes [2]. The

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terms post stroke shoulder pain and hemiplegic shoulder pain (HSP) are commonly used but are simply descriptive and do not point to the underlying contributory pathologies that represent potential therapeutic targets [3]. Stroke clinicians often lack confidence in identifying the underlying causes of PSSP, which in turn hampers effective management [4,5].

Shoulder pain results from a complex interaction of biopsychosocial processes [6], but for practical purposes the best starting point is to consider pathologies that are either local or remote (including referred pain) to the shoulder complex (Figure 1). This article will focus on understanding and treating frozen shoulder in the hemiparetic arm, a common pathology that influences structures local to the shoulder complex.

Frozen Shoulder clinical presentation

Frozen shoulder affects 2-5% of the general population and is most common in people between 40 – 60 years old [7,8,38]. In the hemiparetic shoulder after stroke it has been shown to account for between 41% to 88% of cases of pain [9,10,11]. Frozen shoulder is usually a clinical diagnosis characterised by (i) pain on movement and (ii) at least 50% restriction in passive external rotation of the shoulder compared to the non-paretic side [12]. Another diagnostic criterion that has been used is; at least 30% restriction in 2 out of 3 of passive movements; external rotation, internal rotation and abduction of the shoulder [13]. It is important to exclude bone pathology as a differential diagnosis of passive shoulder restriction with plain shoulder x-rays, especially if the subject has experienced trauma.

Frozen shoulder usually starts with a pain predominant phase, likely inflammatory, characterised by pain on movement and/or at night [8,14]. This is followed by a restriction predominant phase with reduced pain but with significant passive joint restriction [8,14]. Often, frozen shoulder is self-limiting and improves with time, though time scales can be highly variable and can be several years [14]. This means early intervention to treat frozen shoulder in stroke survivors is vital to prevent disruption to rehabilitation and helping to optimise upper limb recovery.

Frozen shoulder pathophysiology

What causes the observed restriction pattern?

The shoulder joint is anatomically complex. The glenohumeral joint has multiple degrees of freedom because of a small area of bone articulation [16] and joint stability is largely provided by muscle control and a ligamentous capsule [16]. For example, the axillary pouch of the capsule becomes tense in abduction and elevation to prevent excessive movement [17]. The coracohumeral ligament provides anterior stability [17]. In cases of frozen shoulder, fibrosis of these structures reduces the capsule volume and results in passive shoulder external rotation and abduction restriction [10]. In regard to other potentially affected structures; fibrosis of the superior glenohumeral ligament results in restriction of shoulder external rotation when the humerus is abducted to 90 degrees [18]. Inferior posterior capsule fibrosis can result in restriction of shoulder internal rotation [18].

Contrast enhanced MRI and arthrogram imaging of the hemiparetic frozen shoulder often show thickening in the coracohumeral ligament and joint capsule axillary pouch [9,10,].

What causes capsule fibrosis?

Rotator cuff tendinopathies and tears are more common in the hemiparetic shoulder [19,11] and associated age-related tendinosis may make tendons even more susceptible to injury [20]. Soft tissue injury creates a pro-inflammatory environment which can disrupt joint homeostasis within the shoulder capsule, especially in those with micro-vascular co-morbidities such as diabetes mellitus [21,22]. Advanced glycation end products (AGEs) which accumulate in shoulder tissues during ageing and as a result of diabetes, may also promote a pro-inflammation environment [38]. Inflammation can disrupt the balance of enzymes that regulate the joint extracellular matrix [21]. For example, matrix metalloproteinase (MMP) is responsible for degrading collagen as part of the joint remodelling process [21] and is regulated by the tissue inhibitor of matrix metalloproteinase (TIMP) [21]. In cases of frozen shoulder, MMP/TIMP ratios are reduced [23] resulting in collagen fibrils being continuously laid down leading to thickening of the ligamentous joint capsule. As well as fibrosis, inflammation may also trigger neo-angiogenesis and neo-innervation around the joint capsule [14,38]. This hyper-vascular synovitis near nerve endings may explain why frozen shoulder is so painful in the early stages [7].

The challenge of identifying cases of frozen shoulder in hemiparetic shoulder

Diagnostic criteria for frozen shoulder have been developed in the non-neurological population, but there are additional diagnostic challenges in the post-stroke hemiparetic arm. After stroke, another major cause of restriction of external rotation and abduction of the shoulder after stroke is spasticity in the shoulder internal rotators [10], which can develop within days of stroke when the arm is very weak [24]. Restriction can also be due to non-neural muscle and soft tissue shortening as well as altered movement patterns [25,26] making a single diagnosis difficult. To make things more challenging some stroke survivors with proximal shoulder motor activity can develop guarding in shoulder internal rotators/adductors. This guarding has been shown to mimic frozen shoulder restriction patterns in the general population [46]. These different causes of restriction often coexist and so a diagnostic hypothesis is usually a 'best guess' of the primary cause after careful assessment. Hypotheses can then be updated by

Local Direct Causes
Frozen shoulder
Tendinopathy
Bursitis
Muscle injury
Peripheral nerve Injury
Bone injury
Arthritis
Ligament injury
Proximal spasticity
Heterotopic ossification
Joint contracture

Remote Direct Causes
Central post stroke pain (Lesion in pain modulating structures e.g. Thalamus/Medulla)
Autonomic dysfunction – Complex Regional Pain Syndrome/ Shoulder Hand Syndrome
Spinal referred pain
Visceral referred pain

Indirect factors that may influence pain perceived at shoulder
Age
Diabetes, Hyperthyroidism and other chronic conditions
Lifestyle - Upper limb involvement in profession and levels of sedentary behaviour
Psychosocial Factors – Mood / Anxiety/ Prior experience
Subluxation related traction forces
Spasticity related compression forces
Poor joint protection/handling
Cognitive or communication impairments

Figure 1: Possible local and remote sources of pain perceived at hemiparetic shoulder after stroke [9,11,19,30,44].

reassessment after initial treatment approaches are trialled.

If frozen shoulder is suspected from clinical assessment, evidence of glenohumeral joint effusion and thickening around the ligamentous capsule on soft tissue imaging (ultrasound or MRI) can add weight to the diagnosis of frozen shoulder [9].

Diagnostic Nerve Blocks

In cases where proximal spasticity of shoulder adductors and frozen shoulder occur together, identifying the dominant pathology may be aided by a diagnostic lateral pectoralis nerve block (DNB) [27]. The lateral pectoralis muscle supplies the pectoralis major muscle and so improvements in range after DNB indicate spasticity in the pectoralis major is the predominant cause of restriction. If range does not improve, frozen shoulder or contracture is then identified as the most likely cause of pain and restriction [27]. However, additional shoulder internal rotators/adductors such as subscapularis, latissimus dorsi and teres major are also known to develop spasticity post stroke [43]. These muscle groups would be unaffected by this nerve block, indicating that there is a risk of misinterpreting the results of DNBs.

Differentiating between frozen shoulder and proximal spasticity of shoulder internal rotators currently still relies on a detailed multidisciplinary assessment, which will establish a working diagnostic hypothesis. This is followed by trialling treatment approaches in a systematic way. Further research is required to refine diagnostic techniques to aide differentiation between these common presentations.

Treating Frozen Shoulder in the hemiparetic arm

Most of the rationale for treating hemiparetic frozen shoulder comes from experience in the general population. Education to prevent or reduce any fear of movement and promoting engagement in regular daily hemiparetic shoulder movements is key to improvements in symptoms and shoulder range [28,42]. These can be conducted independently or with the support of carers. In the general population with frozen shoulder, stretching several times a day into external and internal rotation, flexion and abduction improves pain, joint range and strength and is more effective than passive pendular exercise [23]. Stretching dosage will depend on an individual's pain tolerance, and pain irritability (length of time pain remains after movement) which will usually coincide with the suspected frozen shoulder phase (pain predominant versus restriction predominant) [38]. It may be necessary to start programmes more conservatively, for the first few days to build confidence. Analgesia should also be considered to assist tolerance of regular arm movement [38]. Care should be taken to optimise alignment in the presence of subluxation, with adequate support of the arm. This relies on training of the patient's support network to ensure movements are safe and appropriate.

Twelve weeks of stretching into tolerable pain for 10 seconds, 4 times a day has been shown to improve joint homeostasis in the general population by returning serum levels of MMP and TIMP levels to normal [23]. In stiffness predominant cases where there is no suspected inflammation, heat treatments in combination with passive stretching may help to improve range further [23]. The following injection treatments can provide a window of opportunity for physical interventions.

Intra-articular steroid injection has proved to be effective for pain reduction and subsequent functional improvements in the general population diagnosed with frozen shoulder [29]. Published literature for steroid injection in hemiparetic shoulders has shown mixed results [30]. However, pain presentations in these studies are often poorly defined, with hemiplegic shoulder pain (HSP) used as a blanket diagnosis [30]. Steroid injections may be more effective in pain predominant cases of hemiparetic frozen shoulder when inflammatory processes are particularly active.

Hydrodilatation/hydrodilation injections involve combining a local anaesthetic and a high volume of saline (usually between 20-30ml), with or without a steroid, to distend the capsule [14]. Hydrodilatation has a greater effect on reducing early pain compared to steroid alone in frozen shoulder cases in the general population but long-term functional improvements appear to be similar with both treatments [29]. Steroid injections can result in transient reductions in rotator cuff tensile strength and can influence tendon and collagen cell viability [31], but serious adverse events are rare [36,37]. Deciding whether an injection is appropriate should be guided by levels of pain on movement, at rest and overnight, and whether initial stretching alone is effective.

Suprascapular nerve block (SNB), can provide a window of pain relief to allow engagement in upper limb movement, especially in cases where steroid injection is not possible or indicated. This is because the suprascapular nerve is believed to supply around 70% of sensory innervation of the shoulder [39]. As spasticity is modulated by sensory inputs; SNB may also help to reduce local tone [28,41].

If restriction is significantly impacting on engagement in a stroke survivor's activities of daily living and the treatments discussed are ineffective there may then be a case for referring them for arthroscopic capsular release (ACR) or manipulation under anaesthetic (MUA) [47,48].

Finally, it is important that as pain improves, a progressive shoulder strengthening programme is established, especially involving activation of the rotator cuff [33]. Away from the shoulder, strengthening of the trunk and lower limbs in functional training can also help improve axioscapular muscle recruitment, which will likely help to prevent reactivation of frozen shoulder processes [35]. In cases where strengthening is not possible because of dense weakness, Neuromuscular Electrical Stimulation (NMES) is a good alternative to consider [30].

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Future Research

1. Improving diagnostic accuracy so treatments can be based on mechanistic principles: It would be beneficial for future clinical trials to target the underlying causes of restriction and pain in the hemiparetic arm. This might involve a combination of diagnostic nerve blocks, spasticity assessments, x-rays, ultrasound, blood tests or contrast enhanced MRIs [9,27]. Better understanding of the natural history and clinical presentation of different pain pathologies will help target treatments to appropriate patients based on mechanistic principles.

2. Early intervention: Reducing the time to treat leads to better outcomes and reduces chronicity of hemiparetic shoulder pain after stroke [28]. Future studies should focus on the first 3 months after stroke at a time when successful intervention could help prevent lasting contracture or joint fibrosis.

3. Systematic approaches to shoulder pain: Treatment pathways that guide management after assessment, have been shown to improve outcomes [45]. Published pathways have so far concentrated on rehabilitation settings, where cohorts are generally several months post stroke. It would now be useful to trial systematic approaches earlier in the stroke pathway, sooner after pain onset.

4. Anti-inflammatory drugs: There are no human trials targeting the MMP pathway, although this is an area of active research in preclinical models of frozen shoulder [34].

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Stroke Series - Introduction

Intracerebral haemorrhage (ICH) is a particularly devastating form of stroke, affecting over 200,0000 adults around the world each year, and with higher morbidity and mortality than ischaemic stroke. Despite the huge advances in the management of ischaemic stroke, in particular hyperacute reperfusion therapies, effective treatments have historically been limited in ICH. An upcoming series of articles will explore some of the advances in treatment of ICH over the next few editions beginning with articles on the acute management of ICH.

We will kick off the series from Manchester with Alastair Paterson and Adrian Parry-Jones highlighting the latest evidence on the medical management of patients presenting with ICH in the hyper-acute phase and the need for often basic but timely intervention.

Surgical management of ICH remains uncertain despite research addressing technique, technology, and timing and intervention is typically decided on a case by case basis. Chris Ovendon, Tim Kleinig and Amal Abou-Hamden from Adelaide will be presenting an update on acute ICH addressing current research on surgical techniques.

I encourage you to read these articles highlighting the latest evidence ranging from a more intensive approach to basic care to advances in surgical techniques for patients suffering from this common and devastating neurological disorder

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Hyperacute Medical Management of Intracerebral Haemorrhage

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Abstract
Intracerebral haemorrhage (ICH) is caused by spontaneous, non-traumatic haemorrhage within the brain parenchyma. ICH has poor outcomes, with a 30-40% 1-month case fatality and most survivors remaining dependent. Current management of ICH is aimed at providing appropriate supportive care and reducing the risk of haematoma expansion, which affects up to 20-30% of patients in the first 24 hours. Rapid and intensive blood pressure lowering to a pre-specified target and reversal of anticoagulants in the 20% of patients who are taking them may reduce the risk of expansion and improve outcome.

Intracerebral haemorrhage (ICH) is caused by spontaneous, non-traumatic haemorrhage into the brain parenchyma and globally accounts for 27.9% of incident strokes, 44% of 6.55 million stroke deaths and over half of the disability burden caused by stroke [1]. Little change in case-fatality rates within the first 48 hours of ICH onset have been seen [2]. Current treatment for ICH seeks to reduce the risk of haematoma expansion (HE), an early complication affecting up to 20-30% of ICH patients in the first 24 hours which is associated with increased morbidity and mortality.

Time since symptom onset, haematoma volume on baseline imaging and the use of anticoagulant or antiplatelet drugs at onset are all associated with a higher risk of HE. Intensive blood pressure (BP) lowering reduces haematoma expansion and along with rapid, early delivery of anticoagulant reversal, these interventions form the mainstay of acute ICH medical treatment. The antifibrinolytic agent tranexamic acid and the haemostatic drug recombinant factor VIIa (rFVIIa) reduce haematoma expansion, but have not proven overall clinical benefit in phase III clinical trials to date [3–5].

Provision of appropriate supportive care and referral of patients for neurosurgery may also be of benefit, the latter covered in another article in this series.

Reversing Anticoagulant Medication

Several trials have proven non-inferiority of direct oral anticoagulants (DOACs) over warfarin, a vitamin K antagonist (VKA), for stroke prevention in atrial fibrillation [3,6–8]. Lower rates of major haemorrhage and ICH are seen in patients prescribed DOACs compared with VKAs.[9] The treatment of serious bleeding associated with DOACs and VKAs is by administration of either: 4 factor prothrombin complex concentrate (4F-PCC), vitamin K, idarucizumab,

Table 1: Reversal agents for commonly used oral anticoagulants

Oral Anticoagulant	Pharmacology	Reversal agent	Trials / Studies
Warfarin	Vitamin K antagonist	Vitamin K (phytomenadione) + 4F-PCC	INCH*[13]
Apixaban Rivaroxaban Edoxaban	Factor Xa inhibitors	4F-PCC OR Andexanet alfa	Meta-analysis[14] ANNEXA-4†[15]
Dabigatran	Direct thrombin inhibitor	Idarucizumab	REVERSE-AD‡[16]

**Fresh frozen plasma versus prothrombin complex concentrate in patients with intracerebral haemorrhage related to vitamin K antagonists (INCH) trial[13]; †Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study[15]; ‡Idarucizumab for Dabigatran Reversal (REVERSE-AD) trial[16]*

or andexanet alfa, depending on which anticoagulant has been used (Table 1) [10]. Correction of coagulopathy by reversal of anticoagulant medication has been linked to a reduction in HE [11]. Failure to reverse an elevated INR within 2 hours of admission is associated with an increase in morbidity and mortality [12].

VKA Reversal

VKA antagonists lead to the synthesis of ineffective clotting factors FII, FVII, FIX and FX, and anticoagulant proteins C and S. Reversal of VKAs therefore requires intravenous replacement of these factors by administration of 4F-PCC, and vitamin K (phytomenadione) administration [17]. The INCH trial found 4F-PCC to be superior to fresh frozen plasma (FFP) in normalising INR in patients with ICH [13]. Factors in 4F-PCC are 8-16 times more concentrated than in normal blood plasma and FFP, reducing the infusion volume required [18]. The use of 4F-PCC is associated with a reduced risk of 30-day mortality compared to no treatment [19].

Most national and international guidance recommends vitamin K and 4F-PCC. For example, ESO guidance (2019) recommends reversal of anticoagulation if the INR >1.3. Varying doses of 4F-PCC are recommended depending on the INR, with FPP indicated as second-line. Vitamin K (10mg IV) is always indicated, and repeat INR is advised at 12-24 hours [20]. (Figure 1)

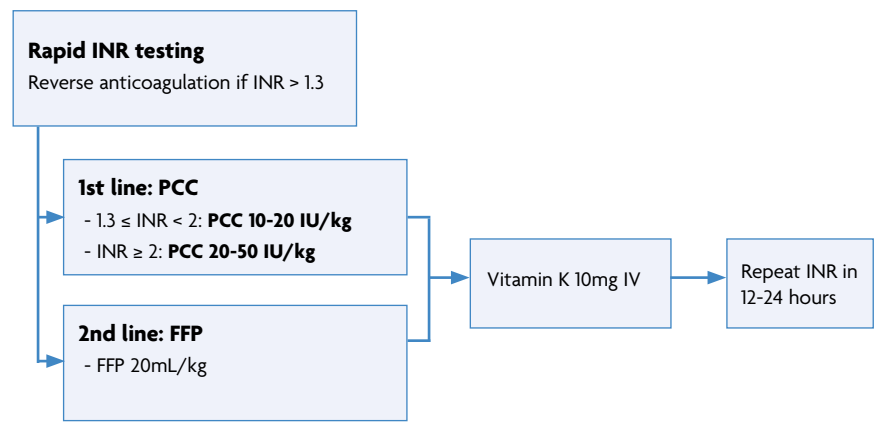

Figure 1: Flowchart for reversal of Warfarin (Adapted from ESO guidelines)[21]

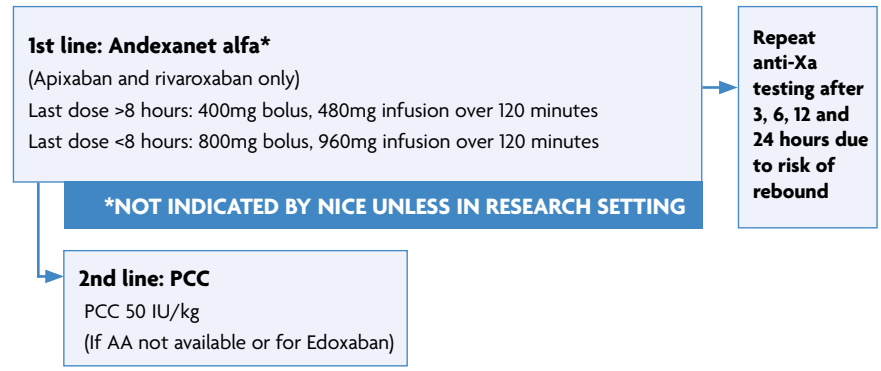

Figure 2: Flowchart for reversal of Xa inhibitor therapy (Adapted from ESO guidelines)[20]

Factor Xa Inhibitor Reversal

Apixaban, rivaroxaban and edoxaban are factor Xa (FXa) inhibitors in common use. FXa inhibition prevents the FXa mediated conversion of prothrombin (II) to thrombin (IIa) [22]. 4F-PCC may be useful in replenishing FXa levels, but it does not prevent the pharmacological action of FXa inhibitors.

Andexanet alfa (AA) is a recombinant form of human factor Xa, modified to reduce its prothrombotic activity whilst retaining its Xa inhibitor binding affinity [15]. It therefore acts as a decoy receptor, binding to Xa inhibitors and preserving the function of factor Xa [23]. Although AA shows haemostatic efficacy in 90.9% of ICH patients taking apixaban and rivaroxaban [22,23], the cost of treatment stands at around $15,000 per patient [25]. NICE only recommends AA for reversal of anticoagulation in cases of life-threatening or uncontrolled gastrointestinal bleeding. NICE does not recommend the use of AA in ICH except for the purposes of research [26], as the ANNEXA-4 study under which market authorisation was applied for was a single-arm trial with high risk of bias, and was not deemed to provide sufficient evidence of cost-effectiveness [15].

The anticipated publication of the ANNEXA-I randomised controlled trial in 2025 is hoped to bring greater clarity.[27] Where AA is not available, or for factor Xa inhibitors other than apixaban and rivaroxaban, ESO and AHA guidelines recommend the use of 4F-PCC (37.5-50 IU/kg) [20,28].

Direct Thrombin Inhibitor Reversal

Dabigatran is a direct thrombin inhibitor. Reversal of this agent is with idarucizumab (Praxbind), a monoclonal antibody fragment. Both ESO and AHA guidelines recommend the use of idarucizumab for dabigatran therapy reversal (2 x 2.5g IV) as it was found to completely reverse the anticoagulant action of dabigatran within minutes of administration in the RE-VERSE AD trial [16].

Blood Pressure Lowering

The implementation of intensive BP lowering appears to reduce HE when compared with guideline treatment, although this reduction is not associated with any improvement in functional recovery at 3-6 months [29]. A number of trials have examined the impact of systolic blood pressure reduction on death and disability, using a range of approaches and agents [30–35].

Two key trials, INTERACT-2[30] and ATACH-2 [36], produced conflicting results, reporting a marginal reduction versus no reduction in death and major disability respectively. Participants in ATACH-2 had a larger SBP reduction, which may have increased the risk of adverse events in this trial. In a pooled analysis of the two trials, Wang et al. identified a J-shaped curve between SBP reduction and odds of a poor outcome at 90 days. This demonstrates that while improved outcomes were seen in SBP reduction up to 32mmHg, this association began to reverse at 46mmHg, and a SBP reduction of >72mmHg was associated with a poor outcome.

The risk of Acute Kidney Injury (AKI) more than doubled where SBP reduction was >90mmHg, compared to <90mmHg. In patients with CKD, this risk almost quadrupled [37]. Larger decreases in eGFR were associated with AKI and higher modified Rankin Scale (mRS) scores [38]. Most guidelines recommend the intervention tested in INTERACT-2 or something similar - that is to reduce the SBP to < 140 mmHg within 1 hour for patients presenting within 6 hours of onset and with an SBP > 150 mmHg [39–41]. Due to a lack of evidence, optimal management for patients beyond 6 hours and for those with unknown time of onset is not clear thus guidelines vary in their recommendations.

Supportive Care

Fast, evidence-based, proactive and targeted control of haemodynamics and blood pressure whilst considering neurosurgical input has been linked to improved outcomes. The delivery of an 'ABC' care bundle (Anticoagulant reversal, BP lowering, Care pathway for referral to neurosurgery) at one stroke centre in the UK was associated with a reduced needle-to-target time for BP reduction and a reduced 30-day case-fatality rate [42]. Lower rates of early do not resuscitate (DNR) orders and improved access to critical care were also observed in this study [43].

Meta-analysis data supports the management of ICH in specialist stroke care settings: a greater reduction in mortality was seen in patients with haemorrhagic stroke than ischaemic stroke when both groups were treated on stroke units [44].

Conclusion

The medical management of ICH is focused on reducing the risk of HE through reversal of anticoagulants and intensive BP lowering. Improving the management of ICH is not solely limited to newer and more costly medications. Improving the timeliness and intensity of care in relation to BP management and anticoagulant reversal whilst assigning patients to the appropriate care pathways shows promise for future hyperacute care in ICH.

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Update on MR guided focused ultrasound for tremor

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Abstract
Transcranial MR guided Focused ultrasound (MRgFUS) is a recently approved treatment for patients with Essential Tremor (ET), the commonest movement disorder in clinical practice. In this review, we explain why thalamotomy has returned, how it is performed, and outline the basic eligibility criteria and risks of this procedure. The aim of this article is to provide a practical guide to clinicians seeing ET patients as to what they should consider before referring for this treatment.

In November 2020, NHS England published its commissioning document endorsing the treatment of 150 Essential Tremor (ET) patients a year with Transcranial MR guided Focused ultrasound (MRgFUS). This was remarkable, not only for its timing – its appraisal of the evidence and eligibility criteria were produced at the height of a global pandemic - but also for its endorsement of a treatment by the largest public provider of health care in world, that had hitherto been reserved to a small number of private institutions in North America and Continental Europe. Some might consider this decision to be the product of commercial and patient pressure. In this update, however, we will argue that this was the correct decision, for patients, clinicians and ultimately for the understanding the longer-term role of minimally invasive forms of neurosurgery for neurological symptom control.

Why the return of lesioning?

The therapeutic effect of MRgFUS is achieved by performing a thalamotomy. In this respect, there is nothing "new" about this treatment. Lesioning the thalamus for the relief of tremor is nearly as old as functional neurosurgery itself. Furthermore, ultrasound brain lesions were attempted and quickly abandoned in the 1950s [1].

For many, reports of MRgFUS thalamotomy begged the obvious question of, why? The idea of a return to lesioning seems regressive – were we repeating the mistakes of past generations rather than learning from their experience? Surely thalamotomy went "out with the Ark," and rightly so, given the unacceptable levels of permanent adverse effects when compared head-to-head with the "reversibility" of Deep Brain Stimulation (DBS) [2]. Like many changes in clinical practice, the reasons are rarely singular and are both obvious and at the same time harder to define. High re-implantation rates [3], the significant cost savings of MRgFUS [4], and patient or clinician antipathy towards open brain surgery might, in part, explain a demand for alternatives to DBS [5, 6]. Technological fusion of Magnetic Resonance Imaging with an ultrasound transducer system that can achieve sub-millimetre resolution thermal ablation is a good starting point. However, these factors do not explain the uptake of MRgFUS over and above more established lesion-based techniques such as radiofrequency ablation or gamma-knife radiosurgery [7]. The principle reasons are two-fold. For the patient, the clinical effects are immediate. There is no period of post-operative uncertainty awaiting the effects of radio-necrosis or months of follow up appointments optimising DBS settings. MRgFUS relies upon delivering low intensity "sonications" (ultrasound doses lasting 10-20

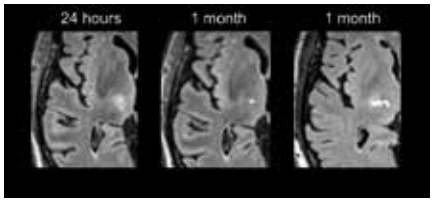

Figure 1 Typical response patterns in one patient to MRgFUS thalamotomy targeting the Ventral intermediate nucleus of the thalamus (Vim) for Essential Tremor. Representative Fluid Attenuation Recovery sequences (FLAIR) at 24 hours (left) with perilesional oedema. This patient experienced transient ipsilateral facial paraesthesia which resolved in parallel with the imaging findings of a discrete thalamotomy lesion at 1 month (middle). For comparison, the post-operative imaging of a different patient who developed permanent gait disturbance and dysgeusia. Imaging at 1 month post-thalamotomy demonstrates at "lateral-tail" [11] recognised as an unpredictable consequence of MRgFUS in 7% of cases.

Table 1 (The NHS England eligibility criteria)

Clinical Eligibility Criteria for MRgFUS Thalamotomy	**Comment**
Patients with Medication-refractory Tremor	Tremor that has not responded to two medications (one of which is first line treatment – propranolol or primidone)
Patients with either a postural tremor or an intention tremor of grade 3 or 4 in the target upper limb (scored using the CRST part A)	Grade 3 tremor amplitude (1 -2cm) grade 4 (>2cm)
A score of 2 or above in any one of its items in the CRST Part C	As a rule patients who need to use two hands to cut with a knife or to hold a drink to their mouth will have a score of 3 or more
Patients who are **not eligible** for DBS	The NHS England DBS commissioning document** defines DBS eligibility as medication resistant ET with significant impairment of function able to undergo general anaesthetic*

CRST = Clinical Rating Scale for Tremor [9].
**https://www.england.nhs.uk/wp-content/uploads/2013/04/d03-p-b.pdf

seconds), at intensities that are sub-lesional with the aim of "mapping" the final intended target of the lesion. During DBS implantation, the number of changes to the electrode trajectory is limited by oedema caused by the electrode tract. In contrast, ultrasound sonications at sub-lesional temperatures can be delivered with a greater spatial freedom to define the final lesion location. This is critical to the success of the procedure as the "eyes" of the surgeon are exclusively guided by feedback from clinical assessment and what the patient experiences. As no meaningful structural imaging can be recovered during the procedure, the heavily clinician led treatment becomes exclusively dependent upon the clinical skills of the neurologist and their communication with the treating surgeon.

Who should be considered for MRgFUS Thalamotomy?

The existing evidence for MRgFUS is supportive of its use in patients with a diagnosis of Essential Tremor targeting the Ventral intermediate nucleus (Vim) of the thalamus[8]. Patients need to be able to tolerate a 2-3 hour period in and out of an MRI scanner making claustrophobia or permanent MR incompatible implants an absolute contraindication. The NHS England eligibility criteria are summarised in Table 1.

The most challenging aspect of applying these criteria is defining who is "not eligible for DBS." It is a straightforward decision to offer treatment to a patient over the age of 75 or one with a co-morbidity that general anaesthesia is a high risk. However, is a 55-year old who is unwilling to consent to DBS given full knowledge of the risk of intracranial surgery ineligible for DBS? This uncertainty places shared, fully informed decision making at the heart of the patient selection process for MRgFUS thalamotomy. It also emphasises the need for a multi-disciplinary approach to ensure that the right patient, despite understandable preference for the "less invasive" option, is offered the correct treatment to ensure the best likelihood of an enduring and robust improvement in their quality of life.

What are the drawbacks of MRgFUS thalamotomy?

A frequent misperception is that MRgFUS is non-invasive. Relative to open surgery this is true, however, intra-cranial oedema (Figure 1) frequently leads to transient balance and or sensory side effects. Persistence of these can be attributed to lesion extension outside of the target zone [10]. In the pivotal trial of Elias et al., [8] these occurred in over 30% of patients (objective or subjective gait disturbance 36%; paraesthesia/numbness; 38%) persisting at 12 months in around 10% (gait 9%, sensory 14%). These relatively high rates have been replicated in the largest published series [11] with persistent dysarthria observed in 6%. Improved understanding of the relationship between the ultrasound dose and lesion size [11], advances in targeting [12] and intraprocedural imaging, are likely to lead to further reductions in adverse effect profile. However, there remains uncertainty as to what factors explain unpredictable "hyper-response" [7, 11, 13] which occurs in 7% of treatments. These are associated with "lesion tails" which extend into the internal capsule associated with high level of permanent adverse effects [11]. Accordingly, excluding patients with pre-existing balance and/or gait disorder is considered best practice and is reflected in existing guidelines. This can mean that many patients who have severe ET are excluded based upon gait abnormalities which are a common "soft" sign in ET [14]. The risk of permanent gait disturbance also needs to be considered in younger ET patients who are unwilling to consent to the risks of DBS. A handful of patients have gone on to have DBS following MRgFUS [15, 16], however, in the worst-case scenario, permanent side effects from a MRgFUS treatment may eliminate DBS as a follow on "rescue" therapy.

MRgFUS exclusively aims at improving (typically dominant) limb tremor. Head and voice tremor do not respond to unilateral treatment [8] so patients with more axial tremor symptom burden may be more appropriate for DBS. Historical concerns about risk of dysarthria from traditional thalamotomy have led to considerable caution when performing bilateral MRgFUS thalamotomy[2]. Results from a recently published trial where bilateral ultrasound thalamotomy was performed at least a year after the first hemisphere was treated, look promising from a safety point of view [17]. However, experience is so limited that it should not be considered outside of a research context.

Most patients receive a significant improvement in tremor control in the treated limb. In around 10% [18] the tremor returns to baseline levels and one third see less than 50% improvement at two-year follow up [19]. Re-treatment is possible but is technically more challenging at the second attempt at thalamotomy. It is important therefore, for patient expectations to be adequately managed pre-treatment in the event of treatment failure.

What is the future likely to hold for MRgFUS?

One of the biggest outstanding questions is whether MRgFUS has a role in the treatment of non-ET tremor syndromes. Tremor dominant Parkinson's disease (PD-T) being the most obvious indication. The existing evidence is limited in quantity and quality to support its use in PD-T outside of clinical research [20, 21]. To date, outcomes from MRgFUS thalamotomies in PD-T show similar safety profiles to ET studies but much greater treatment variability. Notably, no long-term follow-up data is available to inform whether the clinical effect is durable. Whether these limitations of MRgFUS in PD-T reflect difficulties in selecting patients from a heterogeneous disease group (cf. ET), or uncertainty as to the most efficacious target for tremor, are questions subject to ongoing research investigations [22]. It seems likely, with the appropriately rigorously designed clinical studies, these questions will be more clearly answered and a new treatment option available to other patient groups who experience life limiting tremor.

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David Marsden (1938-1998): contributions to cognitive neurology

Abstract
Professor C. David Marsden (1938-1998) made major advances in the understanding of movement disorders during his illustrious career prior to his untimely death 25 years ago. In addition to this body of work, he also made contributions to the understanding of cognitive functions in these disorders, necessarily so in view of the neuropsychological overlap of cognition and movement. This article briefly summarises Professor Marsden's clinical contributions to cognitive neurology, some of which still inform clinical practice today.

For neurologists of a certain age, it may come as something of a surprise, if not a shock, to realise that 2023 will mark a quarter of a century since the untimely death of Professor CD Marsden. This surprise may, in part, be related to the fact that publications bearing the Marsden imprimatur continued to appear long after his death, culminating in the eponymous *Marsden's Book of Movement Disorders* [1] which, though contemplated many years earlier, did not make its first appearance until late 2011/early 2012.

David Marsden is rightly known for his influential contributions, clinical, neuroscientific and administrative, to the field of movement disorders (one of his obituaries described him as "Master of Movement"), but his interests were not limited by this specialisation. As a consequence of his numerous collaborations, he was an author on many papers pertaining to cognitive function and its disorders, either directly or indirectly. A brief review of some of these is given here, restricted to clinical reports, in part to commemorate but also to illustrate the breadth of Marsden's contributions. It should be emphasised that this review does not claim to be exhaustive, and is given from the perspective of an outsider, not someone who ever worked in any capacity for Professor Marsden. An account from those who knew and worked with him is published [2], which briefly alludes to his studies of cognitive deficits in parkinsonian disorders (p.212).

1. Dementia

"Presenile" dementia

One of Marsden's earliest publications, dating from 1972, was based on work undertaken as, according to the paper in the *BMJ*, Senior Registrar at Queen Square, on the subject of (so called) "presenile" dementia [3]. Working with Michael Harrison (d. 2019), a retrospective study of more than 100 patients was presented, in whom intellectual impairment was confirmed in 84 and a "final" diagnosis established in 36. Aside from "cerebral atrophy of unknown cause" (n = 48), many presumed to have Alzheimer's disease or Pick's disease, intracranial space-occupying mass lesion and arteriosclerotic dementia were the next most common diagnoses (both n = 8).

Of the 22 patients classified with no or uncertain dementia, depression was the most common diagnosis. This study predated the availability of CT brain scanning; lumbar air encephalography was the most sophisticated neuroimaging investigation available. Moreover, the initial paper gave neither a definition of "presenile" nor details of the age of the patients investigated; the latter information emerged in a subsequent letter (age range 34-78, mean 61 years) [4].

"Senile" dementia

Patients with "senile" dementia, meaning onset over 65 years of age, formed one group, along with Parkinson's disease and "cerebral arteriosclerosis," in a 1974 study examining clinical features and response to levodopa. Evidently, the dementia patients were in the severe stage of disease, frequently unable to walk or stand; half of them reportedly had "whole body akinesia". Predictably, they did not respond to levodopa, and indeed as a group they showed deterioration in rigidity when treated [5].

Cortical versus subcortical dementia

Distinction between dementia ascribed respectively to cortical or subcortical pathology enjoyed something of a vogue in the 1980s and 1990s. So called cortical dementia was typified by the classical syndromes of amnesia, aphasia, and agnosia, whereas so called subcortical dementia, a terminology first used in the context of progressive supranuclear palsy, was typified by cognitive slowing, sometimes with apathy and depression. Brown and Marsden's review of these concepts, in the context of Alzheimer's disease, Parkinson's disease and Huntington's disease, found more overlap than separation in deficits between the patient groups, hence casting doubt on the functional independence of these two broad diagnostic categories [6].

Alzheimer's disease

Alzheimer's disease (AD) was not an area of particular clinical interest for Marsden but was encountered from time to time in the context of concurrent movement disorder. He was one of the authors on papers describing the alien hand sign [7] and frontal gait impairment [8] in patients found to have underlying Alzheimer's disease pathology. In the first of these reports, the patient had a clinical diagnosis of corticobasal degeneration prior to the availability of neuropathological findings [7] (hence what might now be termed corticobasal syndrome). In the second paper, the one patient in whom neuropathology was available had histological features of corticobasal degeneration as well as AD pathology, the latter most evident in the occipital cortex with relative sparing of the hippocampus [8]. Alzheimer-type changes were also observed along with cerebrovascular pathology in a patient presenting with a late onset generalised chorea [9].

A group of patients with "probable dementia of Alzheimer type" was investigated with tests of visual memory and tests sensitive to frontal lobe dysfunction as a comparator group for patients with Huntington's disease (vide infra) matched for "level of dementia," as defined by Mini-Mental State Examination (MMSE) score. The AD patients were found to be more impaired on tests of recall but superior on the tests sensitive to frontal lobe dysfunction than the Huntington's disease patients [10].

2. Cognitive features of movement disorders

It is perhaps easy to forget from our vantage point that the differentiation of Parkinson's disease from other parkinsonian disorders, sometimes labelled as "atypical parkinsonism" or "Parkinson's plus," was not so clear-cut in the late 1970s/early 1980s, when Marsden and his colleagues began publishing on the subject, than is now the case.
Certainly one of the debts we owe to them relates to the empirical studies which clarified this differential, including cognitive features.

Parkinson's disease

Whilst Charcot, unlike James Parkinson, had recognised that cognitive impairment could be a feature of the disorder upon which he had bestowed the eponymous label of Parkinson's disease (PD), relatively little attention was paid to this aspect of PD until the 1970s and 1980s. Marsden's engagement with the cognitive consequences of PD was evident in a *Lancet* review co-authored with Richard Brown

published in 1984 examining dementia in PD [11]. A downward revision of the frequency of dementia in PD from 1 in 3 to a more conservative 1 in 5 was suggested, in part due to diagnostic errors in distinguishing PD from other akinetic-rigid syndromes. This conclusion was based on the data then available, whereas subsequent studies have suggested a much higher cumulative frequency of cognitive impairment in PD.

As for the specific cognitive features encountered in PD, Marsden was involved in a number of studies examining these, dating back to the early 1970s [5]. Many years later, the cognitive deficits in PD were characterised in comparison to other parkinsonian syndromes, finding slowing in initial thinking time (bradyphrenia) and impairments on tests of frontal lobe function [12].

Progressive supranuclear palsy

In the study comparing various parkinsonian syndromes, patients with progressive supranuclear palsy (PSP) were shown to have cognitive deficits on tests of frontal lobe function, like PD patients, but the greatest deficit in attentional set shifting was found in PSP patients [12].

Multiple system atrophy

Multiple system atrophy (MSA) was generally thought to be free from cognitive dysfunction prior to a report on a "distinctive pattern" of cognitive deficits in MSA of striato-nigral predominance (MSA-P) by Marsden and his colleagues. This showed a prominent frontal-lobe-like component [13], later confirmed in a larger study [12].

Corticobasal degeneration

Marsden and his colleagues were some of the first to undertake systematic studies of patients with corticobasal degeneration (CBD). Understandably this was largely from the perspective of the movement disorders rather than the cognitive features, for example they reported that "Cognitive changes are unusual early in the disease, the intellect being preserved" [14]. Although noting the emergence of aphasia in some patients, there was no apparent awareness of non-fluent aphasic presentations of CBD with subsequent emergence of the typical motor features of CBD, as noted by later authors.

Huntington's disease

The cognitive features of Huntington's disease (HD) were compared to those in AD patients and shown to be distinct, with poorer performance on tests examining frontal lobe function, suggestive of a frontostriatal pattern of dysfunction [10].

3. Other contributions

Apraxia

The nature of apraxia, and the possible role(s) of the basal ganglia in its pathogenesis, was one of Marsden's enduring interests [15]. Apraxia was examined in various parkinsonian patient groups. In CBD severe ideomotor and ideational apraxia was found to correlate with global cognitive impairment [16]. Apraxia was also observed in PSP (three-quarters of patients) and PD (about one quarter of patients) but was not seen in MSA and neuroleptic-induced parkinsonism. Ideomotor apraxia in PSP correlated with cognitive deficit (MMSE scores) and in PD with deficits in frontal lobe related tasks [17].

Amnesia

Early in his clinical career (1974), Marsden was one of the authors on a classic paper showing that posterior cerebral artery occlusion may be a cause of acute onset of amnesia, so called "amnesic stroke," in association with unilateral or bilateral visual field defects. Although diagnosis of these patients was based on clinical evaluation alone [18], the inferences were amply confirmed by later neuroimaging studies. Occasional cases of amnesic stroke are still reported, some with a phenotype apparently indistinguishable from transient global amnesia.

Discussion

Like one of his illustrious predecessors at Queen Square, William Gowers (1845-1915) [19], David Marsden made contributions in the field of cognitive disorders, incidental to his major clinical interests. Since disorders of cognition occur not only in isolation but also as components of more widespread diseases of the nervous system, they may be encountered by clinicians with interests in areas other than cognitive function. The specific pattern of cognitive deficits may be helpful in differential diagnosis. The groundwork of David Marsden and his colleagues facilitated this clinical understanding.

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Franciscus Sylvius: his fissure and aqueduct

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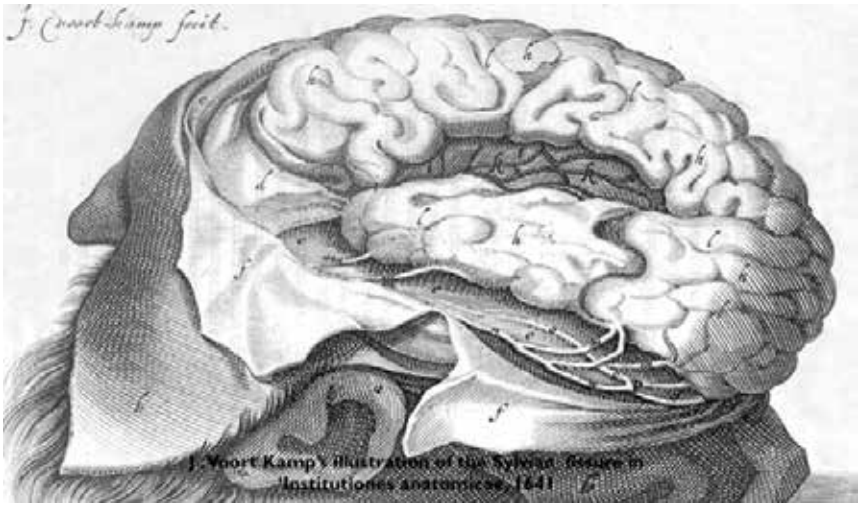

Figure 2. Sylvius's drawing, engraved by J. Voort Kamp in Caspar Bartholin's Institutiones Anatomicae.

Although the name Sylvius is perpetuated by a major cerebral fissure and by the interventricular aqueduct, it is less well known that subsequent to ancient Netherlands alcoholic concoctions, Sylvius distilled the juniper berry with spirits to produce an inexpensive diuretic medicine. It rapidly became popular. He first registered this as "genever"(gin) in 1650. It frequently caused outlandish behaviour, lampooned in William Hogarth's engraving "Gin Lane."

Franciscus de le Boë Sylvius (1614-1672) (Figure 1) was descended from a French family named de le Boë. His family moved to Germany where he was born in Hanau [1], but spent much of his life in the Netherlands. He read medicine at the University of Leiden.

Figure 1. Franciscus Sylvius. Aged 45, portrait by Cornelis van Dalen the Younger (1638-1664).

Coincident with the opening of the University of Amsterdam and with Rembrandt's painting, *The Anatomy Lesson*, Sylvius began his studies in June 1632 and offered a disputation *Positiones variae medicae* in 1634. He obtained his doctorate at the University of Basel in March 1637, defending a thesis, *De animali motu ejusque laesionibus*. According to Albrecht Haller this contained the first description of the lateral cerebral fissure. Sylvius later fully described this fissure and the cerebral aqueduct in 1663 [2] (Figure 2).

He then studied the circulation of the blood and was able to show that it flowed through the blood vessels, pumped by the heart. With his professor, Johan Walaeus, he became a spirited proponent of Harvey's *de motu cordis* (1628).

At Leiden University, Franciscus Sylvius's skills in teaching anatomy earned him fame: "many students, and certainly not the worst ones, attended his courses, so that it seemed as if only he could understand and explain anatomy."

Though mainly devoted to the nervous system, he was the first to describe two kinds of secretory glands: conglomerate, made up of many smaller glands whose excretory ducts unite in a common one, as in the parotid and pancreas, and conglobate or ductless lymphatic clumped glands. In Opera Medica (1679) he demonstrated pulmonary tuberculosis and described how tubercles could progress to abscesses, cavities and empyema in phthisical, consumptive patients.

After nine years at Leiden he moved to Amsterdam in 1641. He practised there until in 1658 he returned to Leiden as Professor of Medicine, where he gave his inaugural lecture *De Hominis Cognitione*. An excellent, enthusiastic teacher he concentrated on the more common diseases in the Caecilia Hospital where Herman Boerhaave (1668-1738) subsequently taught medicine. Sylvius employed Socratic methods applying systems of diagnosis, prognosis, and therapy. He stressed the importance of autopsies as a way of proving or rejecting clinical diagnoses, as well as disclosing the pathology and possible mechanisms of disease.

As an accomplished physician, physiologist, anatomist and chemist, he initiated the 17th-century Iatrochemical School of Medicine [3]. Sylvius regarded as fundamental the effervescent reaction between acid and alkaline secretions, rejecting the classical notion of humours [1,3]. He devised drugs to counteract excesses. But he clung to the ancient notion of the *spiritus animalis* in the blood that was transported by the neck arteries to the capillaries (named by Leonardo da Vinci (1489–1515), their functions elaborated by Marcello Malpighi (1628–1694) and by Antonie van Leeuwenhoek (1632-1723)). The spiritus animalis passed through pores in capillaries into the cerebral cortex, thence permeated the white matter.

Thanks to his excellent teaching, Leiden flourished and attracted students from many countries. His *Disputationem medicarum decas* [1] (1663) contained the theses of several of his students. Shortly before his death on 15 November 1672, Sylvius published the first volume of pathology entitled Praxeos medica idea nova (1671). His pupil Justus Schrader posthumously published the other volumes.

The fissure of Sylvius

Sylvius's accurate study of the cortex emerged from his studies of the brain's blood vessels. He is said to have dissected more than 300 human cadavers whilst in Leiden [4]. One of his students was Thoma Bartholini (1616-1680), son of the famous Copenhagen anatomist Caspar Bartholini. Twelve years after Caspar's death Thoma published the 1641 edition of Caspar's textbook, *Institutiones anatomicae, nouis recentiorum opinionibus et obseuationibus*. It is there that the Sylvian fissure was drawn by Sylvius, engraved by J Voort Kamp (Figure 2). Both Caspar Bartholini and Sylvius had shown and named the fissure separating the temporal lobe from the frontal lobe [5]. Sylvius had earlier made his observations in his thesis of 1637, but did not publish his description. He collaborated with Thoma Bartholini (known for his discovery of the human lymphatic system) in the revision of his father's *Institutiones anatomicae*.

The lateral (Sylvian) fissure is the major groove that separates the superior temporal gyrus from the frontal lobe rostrally and the parietal lobe caudally. Within it lie the small convolutions of the island of Reil, or insula. Sylvius added to his description of the cortical fissures in the disputation *De spirituum animalium in cerebro, cerebelloque confectione, per nervos distributione, atque usu vario*, a thesis [6] defended by the student Gabriel Ypelaer under Sylvius's supervision in 1660. The lateral fissure of Sylvius is described:

> *...the surface of the cerebrum is very deeply marked by gyri which are somewhat similar to convolutions of the small intestine. And especially noticeable is the deep fissure or hiatus which . . .begins at the roots of the eyes (oculorum radices) . . .it runs posteriorly above the temples as far as the origin of the brain stem (medullae radices) . . .It divides the cerebrum into an upper, larger part and a lower, smaller part. Gyri occur along the whole length and depth of the fissure even with the origins of smaller convolutions at the most superior part of it [6].*

He later published his own drawings of the brain in 1663 in Sylvius's Opera as *Disputationes medicarum ad C Bartholini Institutiones Anatomica* [6]. But Caspar Bartholini always gave priority to Sylvius for the discovery. Thoma Bartholinus, in 1640 valued highly Sylvius's anatomical studies and remarked:

> *we can not pass over in silence the very accurate anatomist D. Franciscus Sylvius, since we borrow from his noble brain and ingenuity the admirable new structure of the brain.*

Subsequent descriptions and illustrations of the Sylvian fissure and insula were given by Vicq d'Azyr in 1784 and by JC Reil in 1809 [7].

The aqueduct of Sylvius

The connection between the third and fourth ventricles had already been mentioned or suspected by Galen in *De usum partium* as a canal giving communication between the cerebrum and the cerebellum. Vesalius had clearly described it in *De Fabrica*… (1543) as an anus-like orifice of the meatus which extends from the third to the fourth ventricle below the quadrigeminal bodies (pp.716-717) [7]. In chapter twenty-one of Sylvius's Disputationes medicarum is described a canalis vel aquae-ductus between the conjoined roots of the spinal cord and under "the bridge" (pons Varoli) and the corpora quadrigemina.

Albrecht Von Haller (1708-1777) and Morgagni later commented that the aqueduct had been described before Sylvius [8], first in 1521 by Berengarius Carpensis (c.1465-1530). The term aqueduct was first used by Arantius in 1587 [9]. However Von Haller in his Bibliotheca Anatomica 1774 gave Sylvius credit for his full description.

There was another famous Sylvius, Jacques Dubois (1478-1555), known as Jacobus Sylvius, who taught Vesalius and was an uncritical adherent of Galenic doctrine [10]. Jacobus Sylvius also described the cerebral aqueduct before Franciscus, but nearly twenty-five years after Berengarius Carpensis. He was an important Parisian physician and anatomist, but had a serious dispute with Vesalius who rejected several Galenic edicts.

Franciscus Sylvius was the first to describe the *cavum septum pellucidi* that is sometimes known as the Sylvian or fifth ventricle of the brain [7]. He attracted many students from all over Europe. His most notable students were Thoma Bartholinus, DeGraaf (of the Graafian follicle); Stensen (of Stensen's duct); and Jan Swammerdam, who first described red blood cells in 1678.

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On The Cover...

Our cover image shows a piece of work entitled 'Inverted Venus' by Troika.The piece was exhibited at the recent Cure3 (Cure Cubed) contemporary art fundraising exhibition. Cure3 was established in 2017 and is now in its fourth edition, devised and curated by Artwise in partnership with Bonhams to raise awareness and funds for Cure Parkinson's.

The unique concept for Cure3 centres around each artist being given a bespoke Perspex cube measuring just 20cm3 as a compact space to interact with in any way to create original artworks on or within. The resultant highly sought-after and collectable artworks are exhibited at Bonhams and sold online.

Set up in 2005 by four people living with Parkinson's, Cure Parkinson's is working with urgency to find new treatments to slow, stop and reverse Parkinson's. The charity's funding and innovation has redefined the field of Parkinson's research, enabling the world's leading researchers to prioritise the next generation of drugs for clinical trial.

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SPONSORED FEATURE

Synchronising the Body and Brain Can Bring Harmony to Patients With MS

Dr Agne Straukiene, Consultant Neurologist
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Dr Agne Straukiene is a MS Brain Health 2022 award-winning neurologist with a special clinical interest in MS for 14 years. With a focus on helping patients live a long, healthy, and present life, she is passionate about taking an integrative approach to promote a healthy lifestyle. Dr Straukiene is a founder and host of the BeewellwithMS podcast. She has pioneered a number of digital technology projects and regularly consults NHS, pharmaceutical and digital technology companies. She is also leading on a number of research projects in MS.

Like an orchestra, the connection between the body and brain is a beautiful thing, with no individual organ or emotion playing the composition alone. When one instrument is out of sync, inharmonious chaos can reign and what the musicians are trying to communicate gets lost. For patients with Multiple Sclerosis (MS), symptoms can be experienced across many instruments simultaneously, resulting in the intricate connection between mental and physical health being disrupted and the person feeling helpless and 'out of tune'.

Mental health disorders, such as depression and anxiety are common accompaniments to the physical symptoms of MS, negatively impacting an individual's quality of life.[1] In a study by Marck et al. (2016), it was shown that 32% and 29% of respondents with MS reported living with depression and anxiety, respectively. [2] In an orchestra, the interconnectivity of the instruments to produce a harmonious tune can be influenced by external factors, from a noisy crowd to bad acoustics. The same can be said for a person's mental and physical health being greatly influenced by lifestyle factors including diet, smoking and physical activity.[2,3]

One of the greatest challenges we as healthcare professionals face is encouraging patients with MS to be proactive in adopting coping mechanisms that will help them with any mental health issues they may experience. By withdrawing from co-therapies and MS support services, and not engaging with the full suite of mental health support available to them, patients can experience exacerbated mental and physical symptoms.[4,5]

That's exactly why I strive to follow three steps, 'Listen, Learn, Lure', to ensure a holistic approach during consultations - to not only focus on the instruments playing the wrong notes, but to help the whole orchestra get back in tune.

Listening intently to what patients are telling us comes naturally to many of us in the healthcare profession, although looking for what the patient is not telling us may provide an equally important insight on their mental and physical condition. In today's world where many appointments are carried out virtually, it is crucial for us to treat video consultations as a window into a patient's life. By observing body language, tone of voice and surroundings it can help to determine the patient's emotional state, if they are feeling frustrated or anxious due to their condition, and overall, help to assess their level of engagement with treatment and everyday life.

Learn through the consultation to understand where patients are in their medical journey and assess their readiness to receive support for their mental health. The time constraints of consultations often increase focus on physical symptoms as these can be easier to explain and address. However, by directly asking patients to assess, on a scale of 1-10, their need or readiness to gain help for their mental health, it is possible to identify other therapies adjunct to medicinal treatment that may support their disease management. Asking this question regularly will help determine when to offer these therapies - for example, offering weekly MS exercise sessions to an individual may not be effective if they are in a busy or stressful period of their life as they may not feel ready for a weekly commitment.

Lure patients into positive change by taking time to explain the rewards of self-referral and the benefits that complimentary therapies can have on both mental and physical wellbeing. For example, mindfulness, physical activity, and social connection.

- Research exploring the neuronal explanation of the stress-reducing effects of Mindfulness Based Stress Reduction (MBSR) over 8 weeks demonstrated that MBSR led to changes in the amygdala consistent with improved emotional regulation.[6]
- The effect of combined exercise training was shown to improve Brain-Derived Neurotrophic Factor (BDNF) levels, a molecule shown to play a key role in depression and cognitive impairment, along with balance, functional exercise capacity and fatigue in patients with MS.[7,8,9]
- Additionally, in a study looking at healthy ageing across 600 older MS patients (between ages 55-88), respondents identified social connections, including engagement with support groups and community organisations, as key to helping them live a long and healthy life with MS.[10]

Most crucially, we must encourage patients to fully engage and share the full story of how each instrument is 'playing'. By understanding the full picture, we can then provide the highest level of holistic support, in accompaniment to medical treatment, to help keep all instruments in tune and the orchestra playing in harmony.

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British Society of Physical and Rehabilitation Medicine (BSPRM) – Annual Scientific Conference 2022

Conference details: 12 October 2022. Hybrid event ***Report by:*** Asma Khan MBBS, MRCP(Lon), ST5 NTN trainee, Rehabilitation Medicine, University of Cambridge and Colman Hospital, Norwich, East of England Deanery, UK. ***Conflict of interest statement:*** None declared.

The annual scientific meeting of the British Society of Physical and Rehabilitation Medicine (BSPRM) was held virtually on October 12th, 2022, under its new name. The meeting covered a wide range of intriguing rehabilitation-related topics delivered by eminent speakers.

Long Covid Rehabilitation

The conference began with Dr Manoj Sivan, President Elect of BSPRM, providing a brief overview of the long-term multisystem symptom problem that necessitates the expertise input of a specialist rehabilitation physician in Long Covid services. Dr Joanna Corrado, Clinical Research Fellow in Leeds, then expanded on the features of the long-term multisystem symptom problem, taking a more focused approach into dysautonomia, its prevalence and also discussed the HEARTLOC (heart rate variability biofeedback in Long Covid) research study, which used real-time heart rate variability (HRV) biofeedback and diaphragmatic breathing technique intervention being used in the study.

Following this, Dr Anton Pick, Clinical Director of the Oxford Centre for Enablement, discussed our current understanding of pathophysiology in Long Covid, with particular reference to post-exertional malaise, and limiting factors for physical activity. He then discussed interesting research into the physiology of exercise and tolerance in patients using cardiopulmonary tests with conflicting results.

Emma Tucker, a Specialist Respiratory Physiotherapist at Oxford Health NHS foundation trust, continued the discussion by discussing the practicalities of getting back into physical activity in Long Covid.

Trauma and Amputee Rehabilitation

Dr Moheb Gaid chaired the following session on trauma rehabilitation. Dr Sarah Platt, Clinical Lead for Neuro Trauma ICU at Royal Victoria Infirmary, described the major trauma services and an overview of their role as anaesthetists in trauma ICU. Dr Emily Johnston, a Consultant in Rehabilitation Medicine from the Newcastle Major Trauma Centre, continued the discussion by highlighting the value of rehabilitation prescriptions for a holistic approach.

Mr Jim Ashworth Beaumont, RNOH Stanmore, a Prosthetist and Orthotist, shared his personal story of recovery from polytrauma caused by a road traffic accident that led to a transhumeral amputation during the pandemic. He described the difficulties encountered along the trauma pathway, including lack of early access to a coordinator and the paucity of programmes, but later offered in the rehab prescription that met his requirements. It was fascinating to hear about his experiences with myoelectric or body-powered upper limb prosthetics depending on his functional needs, as well as his thoughts on osseointegration techniques that are presently not offered by the NHS.

Senior Prosthetist at Glasgow's Queen Elizabeth University Hospital, Mr Vincent MacEachern, spoke about the Scottish model for upper limb prosthetics. This paradigm is put into practice, and services like satellite clinics and first trials performed before prescriptions are supplied for upper limb prosthetics as well as other services.

Dr Simon Shaw, Consultant Rehabilitation Physician, Guys and St. Thomas NHS Foundation Trust, provided additional information on prosthetics and the MDT approach with a detailed assessment, equally to address expectations for a prosthetic or non-prosthetic user before prosthetic prescription, and explained the current shortcomings in service as we are still lagging behind other countries in terms of advancing technology hand programme functions.

Community and Cancer Rehabilitation

Soon after the lunch break (with poster viewing), Dr Rohit Bhide, Rehabilitation Medicine Consultant at Sheffield Teaching Hospital, chaired the next session. Professor Diane Playford, Professor of Neurological Rehabilitation, University of Warwick, talked about the burden of community rehabilitation, with overlapping services and systematic gaps that are in need of action and delivered an insightful talk on Best Practice Guidelines in Community Rehabilitation.

Also discussed were problems with how rehabilitation is currently delivered, such as a lack of collaboration among services, overlaps, or gaps in services, and how it might be possible to improve commissioning and deliver high-quality services by identifying gaps and filling them to address a variety of community conditions.

Dr Eugene Chang, Assistant Professor, Division of PM&R, University of Toronto discussed cancer rehabilitation before and after COVID-19 and provided an account of their journey to become one of the top cancer rehabilitation centres. He described the stratification model with the triage system depending on the complexity of cases in cancer survivors and explained how rehabilitation support was given during the pandemic.

Driving After Brain Injury

Dr Inigo Perez-Celerio, DVLA Doctor Driving and Vehicle Licensing Agency, spoke later about the physician's duties in advising on return to driving, with a focus on cases involving traumatic brain injury. He discussed how the fitness advice to drive differs depending on the case's levels of PTA and whether seizures were provoked or unprovoked. If physicians are unsure, they can consult with the DVLA team for additional guidance. Cases can be individually examined and advised, and in some cases, challenges may be made.

PDOC Rehabilitation

The chair of the PDOC Special Interest Group, Dr Judith Allanson, Rehabilitation Medicine Consultant in Putney, presented the session on the pharmacological treatment of people with a prolonged disorder of consciousness (PDOC). Dr Andrew Hanrahan, Consultant at Royal Hospital in Putney, introduced the speaker. The presentation briefly discussed neurochemical mechanisms and outlined the difficulties associated with PDOC research studies. It was encouraging to learn about the SIG's future plans to standardise data collection and prescribing practices.

In Summary

Overall, this conference was packed with information, had variety and was helpful for trainees to learn more about the specialty of rehabilitation medicine, the various services in the country, novel research studies, and other initiatives being made to improve the quality of life of those living with long term conditions and disability.

Encephalitis Conference 2022

Conference details: 1 December 2022, Royal College of Physicians, London, UK (and streamed virtually). Satellite meetings on 30 November. ***Report by:*** Brendan Sargent, Clinical Neuroscience student at Oxford University, UK, and Dr Ava Easton, Encephalitis Society, UK; Dept. of Clinical Infection, Microbiology and Immunology, University of Liverpool, UK. ***Conflict of interest:*** Dr Ava Easton is Chief Executive on the Encephalitis Society.

Event supported by: UCB, SVAR Wieslab, EUROIMMUN, Valneva, University of Liverpool, Quest Diagnostics, Aston University, The Shears Foundation, CSL Behring, The De Laszlo Foundation, Guarantors of the Brain, The Lancet Neurology, Routledge, ACNR

As the world learns to navigate large-scale gatherings in a safe and feasible manner, the 2022 Encephalitis Conference provided an excellent example of a hybrid conference done right. Held at the Royal College of Physicians in London, 409 people attended (140 in person and 269 virtually) from 55 countries worldwide, and included a wide range of professions from neurology, psychiatry, neuroimmunology, psychology, infectious disease, intensive care and emergency medical staff to general practitioners, and other allied health professionals involved in the clinical care or research of encephalitis. This bringing together of individuals passionate about improving care and outcomes in the context of encephalitis and brain infections made for stimulating discussion about important recent and upcoming research.

Included with conference tickets was the virtual satellite meeting on Wednesday 30th November. This included a fantastic session titled 'How to Get Your Grant or Fellowship' hosted by Professor Benedict Michael, Assistant Professor Omar Siddiqi and Dr Mark Ellul, who gave insights into how clinical academics can best apply for funding to support research into encephalitis. They highlighted common pitfalls in writing applications, as well as tips for finding the right funding sources for different individuals. The discussion was made relevant to those from low-middle-income countries and high-income countries; and for junior and senior clinical academics alike. This was an extremely useful session, providing insights into the process and covering aspects of finding funding that are often not taught to researchers.

There was also the Data Blitz Session, in which nine elected conference posters were presented. The authors had the opportunity to discuss their work with the Encephalitis Society's Scientific Advisory Panel, and with the audience, which prompted interesting discussion. The quality of posters was extremely high.

On the morning of Thursday 1st December, delegates were welcomed by Dr Ava Easton, CEO of the Encephalitis Society, and Dr Nicholas Davies, Chair of the Society's Scientific Advisory Panel. The first session was chaired by Professors Arun Venkatesan and Benedict Michael, who seamlessly ensured virtual attendees were involved in questions and discussions, something which was apparent throughout the conference. The first keynote lecture was delivered virtually by Professor Russell Dale of the University of Sydney, on paediatric encephalitis. It set the scene for the day, highlighting important updates in the field, whilst consistently making the talk relevant to clinical practice and outcomes for patients. The discussion after this talk worked well, demonstrating the effectiveness of the hybrid model of conference, a testament to the hard work by Encephalitis Society team in the background.

Dr Cordelia Dunai spoke to delegates about her work in Liverpool on the neurological complications of COVID-19. She discussed the use of inflammatory biomarkers of reduced GCS as well as the application of mouse models in the context of COVID-19. This talk highlighted the importance of the international efforts in researching brain infections, and pointed to exciting work to be done in the future - finding biomarkers that might be used to identify those most at risk of neurological complications.

Professor Romain Sonneville of Université Paris Cité, France, presented results from the EURECA study, highlighting outcomes in adults with severe meningoencephalitis. The results made for sobering listening, and again provided an important backdrop for the conference. For example, it was noted that autoimmune encephalitis was a common subgroup of meningoencephalitis, and that these patients have poor outcomes overall.

The last talk of the first session was an invited guest lecture from Professor Tom Solomon CBE, giving delegates an insight into the journey of studying the impact of steroids on herpes encephalitis, as well as discussing study design and the lessons he has learned from large-scale, collaborative trial implementation. A key message was that in clinical trials, perfect can be the enemy of good; he suggested a focus on pragmatism and practicality. This talk was a useful bridging of the gap between important research fundamentals and clinical knowledge to large scale study design that can impact clinical practice. For those of us early in our careers, this provided helpful insights into the difficulties of large-scale clinical trials. Professor Solomon also discussed exciting future directions, such as the Enceph-IG study (https://www.liverpool.ac.uk/infection-veterinary-and-ecological-sciences/research/groups/brain-infections-group/enceph-ig/).

After some refreshments and viewing of the excellent posters at the exhibition stands, session two was opened and chaired by Professors Frank Leypoldt and Tom Solomon. This session was a great demonstration of the breadth of talks at the conference, starting with exciting neurobiological research and techniques, moving to neuropsychiatric factors in encephalitis and patient perspectives, and global views of encephalitis research. Professor Ana Luisa Carvalho started the session by presenting work on Human anti-CASPR2 autoantibodies and their impact on neuronal architecture. Given the discussion earlier in the day regarding the poor outcomes in autoimmune encephalitis, this presentation regarding how certain antibodies might mediate neurological sequelae, such as via reduction in cohesive neuronal firing, was extremely pertinent.

Associate Professor Federico Iovino then

Associate Professor Federico Iovino

Bursary and seedfunding recipients

presented work on the use of bacterial-neuron interaction blockades in attempting to minimise neurological sequelae after brain infection. This was really exciting work, showcasing methodologies that reduce bacterial adhesion and access to neuronal cells, and thereby might minimise the effects pneumococcal infections can have on the brain. Importantly, although there is more work to be done in this area, the indication that this can have effects on clinical outcomes and neurological sequelae gives hope that these techniques might provide another avenue for clinicians moving forward.

Dr Antonio Farina then discussed immune checkpoint inhibitor related encephalitis, and importantly highlighted stratification of these patients and their outcomes. As a less frequently discussed encephalitis presentation, this was interesting and extremely useful for clinicians and academics alike.

Taking the session from fascinating neurobiological and immunological research to more clinical aspects, Dr Sonali Polakhare presented some work on the neuropsychiatric factors affecting outcomes in encephalitis, which prompted interesting discussion regarding the interpretation of symptomology as side-effect versus part of the core disease process, such as in the context of extrapyramidal side-effects vs movement disorder. For those in the earlier stages of their careers this was an important insight into the nuanced delineation of clinical syndromes in the context of brain infections, and the importance of multidisciplinary discussion to maximise positive outcomes for patients.

Dr Julia Granerod then delivered the second invited guest lecture, speaking about how all the important basic science and clinical work discussed so far translates into epidemiology and public policy to impact global clinical practice. She discussed the importance of availability of resources in the implementation of policy recommendations, and the impact this can in turn have on global research. Highlighting variation in terms of access, treatment and outcomes between countries demonstrated that even as incredible research brings this field forward, there is still work to be done, both in lab settings and political and economic contexts, to ensure patients benefit globally.

After a delicious lunch and some more time to view the posters, Assistant Professor Stacey Clardy and Dr Nicholas Davies opened session three. Ms Marie Vermeiren presented data on long-term clinical outcomes in anti-CASPR2 encephalitis patients, including the tendency for patients to re-present with similar symptoms to their initial presentation, even though across a cohort individuals will have varying symptomologies, essentially demonstrating that new symptoms rarely appear in relapses of encephalitis.

Ms Vasundharaa S Nair then delivered a virtual presentation from NIMHANS in Bengaluru, India, speaking about her work looking qualitatively at the lived experiences of individuals with acute brain infections. This provided an interesting collation of qualitative aspects of encephalitis, highlighting both patients' and carers' perspectives. This aspect is often missed at academic conferences, and provided an important recentering of the purpose of the research being conducted in this field.

Professor Frank Leypoldt presented further research on CASPR2 antibody mediated encephalitis, highlighting the important presentation of orthostatic polymyoclonus. This stimulated interesting discussion regarding the diagnosis and treatment of a rare presentation within a rare, albeit important, disease. Much of this discussion revolved around the use of electrophysiology amongst other approaches, but again this highlighted the important resource discrepancy between regions and the impact this must have on guidelines.

Building again on antibody mediated encephalitis, Professor Carsten Finke delivered a virtual talk on structural and functional neuroimaging in patients with NMDAR encephalitis. Highlighting that NMDA can be considered a molecular mechanism for learning and memory, antibody mediated encephalitis has clear cognitive consequences. He discussed the use of virtual environment navigation assessments to explore patients' executive function and spatial navigation, linking these cognitive outcome measures to neuroimaging measures. It was highlighted that global and hippocampal volume loss after NMDAR encephalitis seems to be reversible, but change in hippocampal connectivity might not recover. This led to interesting discussion regarding whether alterations to functional brain networks might underpin cognitive changes in the medium term – as captured by the spatial navigation tasks. This raised the possibility of using neuroimaging biomarkers in identifying patients at greater risk of cognitive deficits in this patient cohort.

During the final break it was time for the final poster viewing session with some refilling of coffee and tea. The final session of the day was hosted by Dr Ava Easton and Professor Sarosh Irani, and it opened with the hybrid data blitz session of Encephalitis Society funded research: Dr Jamil Kahwagi and Dr Oliver Harschnitz presented their work. After this was the hotly anticipated debate, chaired by Professor Sarosh Irani and Dr Ava Easton. Dr Thomas Pollak presented the house's argument: 'Too many patients with psychiatric illness are being unhelpfully diagnosed with brain autoimmunity'. Dr Pollak pointed out the medical field's propensity for 'MonoCausoTaxoPhilia', an unending excitement for an explanatory story that deals with all patients. He argued that this is almost always unhelpful, and in this context is leading to an epidemic of patients being told their psychiatric diagnosis can be fully explained by brain inflammation. Stepping in to argue against the house, Associate Professor Janet Cunningham laid out excellent arguments highlighting the increasing evidence for autoimmune processes underpinning some patients psychiatric symptoms. Amongst her points, she made brilliant use of Dr Pollak's own published work against him. It was an excellent and stimulating debate. Both parties presented their cases well and responded brilliantly to some tough questions. You could argue that in the end, they were presenting the same argument - that autoimmunity will be explanatory for some but not all patients, and so more research in this area is required to elucidate how we can recognise this aetiology more accurately and promptly.

After the debate, Assistant Professor Stacey Clardy from the University of Utah delivered the final keynote lecture, speaking to the landscape of clinical trials in autoimmune encephalitis. A wonderful talk to follow from the debate, and to finish the conference on, she took the delegates through the large clinical trials in this field, and how the community can move forward. Picking up on Professor Tom Solomon's earlier reference to the aphorism, 'perfect is the enemy of good', Professor Clardy noted that through this proverb we risk complacency in autoimmune encephalitis research. One way she highlighted this was by noting that although mortality in encephalitis contexts has improved, morbidity and lasting disability remains high, as noted by talks throughout the day. A focus on patient experience shows that clinical outcomes still leave much to be desired. This led to discussion regarding avoiding using anecdotal data to support the notion that current practice is 'good enough', to the detriment of improving patient outcomes. Professor Clardy summed this up in the statement, 'as a field we have a tonne of opportunity, but therefore a tonne of responsibility'. This felt like a poignant message to bring the conference towards its close, and an important point for the juniors in this field to keep in mind.

As the day came to an end, the prizes for best oral and poster presentations were given. The quality was extremely high across the board, but special note was given to the winners Dr Sukhvir Wright and Dr Matt Butler for their poster presentations (Peripherally derived monoclonal LGI1 antibodies cause epileptic seizures in a passive transfer animal model and Patients' perspectives on mental health in encephalitis: An international webbased questionnaire study) and Dr Marie Vermeiren for her oral presentation (Long-term clinical outcome and relapse rate in a Dutch anti-CASPR2 encephalitis cohort). Phillippa Chapman, deputy CEO of the Encephalitis Society, showed a video showcasing the work of the Society over the course of 2022, a thanks to all who had contributed, and a call to action moving into 2023 to not only support the work of the Society but also the 10-year anniversary of World Encephalitis Day on 22nd February.

The conference was closed by Dr Ava Easton and Dr Nicholas Davies, followed by a wine reception in the Royal College of Physicians. It was an excellent day, with a wide range of research and topics covered, bringing scientific and clinical work into the context of patient perspectives and outcomes, along with viewing them through the lens of global policy. The conference also acted as a model for hybrid meetings, with a great focus on involving virtual delegates, and the opportunity to rewatch talks for 45 days after the conference. On behalf of all delegates, a huge thanks to the Encephalitis Society team, and everyone who made the day possible.

The next Encephalitis Conference will be held on the 4th and 5th December 2023 at the Royal College Physicians, London, UK and virtually. Sign up for free professional membership to the Encephalitis Society to be alerted to the programme, and other opportunities such as seed funding, grants, and bursaries:

Find out more at: www.encephalitis.info/professional-membership

triMSx webinar – Smouldering MS: what is it and how to approach it?

Conference details: 8 September, 2022. Hybrid event. ***Report by:*** Gavin Giovannoni MBBCh, PhD, FCP (SA, Neurol), FRCP, FRCPath Professor of Neurology, Barts and The London School of Medicine, UK. ***Conflict of interest statement:*** Gavin Giovannoni chaired the webinar.

The fourth *triMSx* webinar, followed by a panel discussion, brought together five global experts and 622 registrants from 71 countries to discuss the latest data on smouldering multiple sclerosis (MS). The event included five succinct presentations, Q&A sessions and polling. This concise format provided convenience to time-poor researchers and clinicians who need to keep up to date with this fast-evolving area while allowing for lively and inclusive debate.

What exactly is smouldering MS?

Should smouldering MS be considered the 'real MS'? This was a question raised following the opening presentation by Professor Laura Airas (Finland) that focused on the definition, pathology and clinical consequences of smouldering MS. Smouldering MS includes MS disability progression in patients who are relapse-free and exhibit neither gadolinium-enhancing T1-weighted lesions nor new or enlarged T2-weighted lesions on magnetic resonance imaging (MRI).

The clinical relevance of smouldering MS is fundamental. Smouldering disease is understood to affect the entire central nervous system (CNS) and is the dominant driver of disability worsening in MS. Smouldering lesions are associated with increased MS severity, more rapid disease progression, brain atrophy, worse clinical disability and worse prognosis, compared with the presence of lesions that are not chronically active.

It is therefore important that healthcare professionals have an understanding of the mechanisms that underlie smouldering MS. Explaining the pathophysiology, Professor Airas showed that compartmentalised, diffuse smouldering inflammation becomes trapped within the CNS. There is reduced trafficking of inflammatory cells from the periphery, and MS pathology spreads outside the focal lesions (which are visible on conventional MRI). Smouldering lesions are also described as chronic active lesions; they are characterised on non-conventional MRI by a full demyelinated core with inflammatory infiltrate around the lesion edge.

Professor Airas also highlighted the critical role of microglia in driving smouldering MS. Microglia are overactivated in a self-propagating cycle, leading to uncontrolled inflammation and chronic progression of neurodegeneration. Diffuse, smouldering inflammation from microglial activation can be detected using specific MRI techniques.

So, a key question is whether smouldering disease is the process involved in all forms of MS? Is it the 'real MS'? The answer to that is probably 'yes', in the opinion of the presenters. The processes driving smouldering MS are most likely present in all patients from the beginning of MS pathology, even before the appearance of clinical symptoms. The clinical phenotypes of MS, namely relapsing–remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS), overlie the pathological process occurring in patients, regardless of the MS designation.

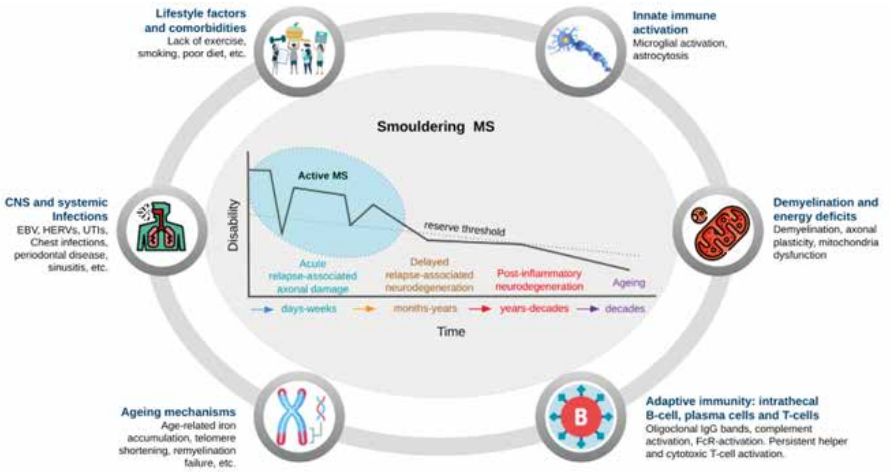

Figure 1. The pathological drivers of smouldering MS. CNS, central nervous system; EBV, Epstein–Barr virus; FcR, fragment crystallisable receptor; HERV, human endogenous retrovirus; IgG, immunoglobulin G; MS, multiple sclerosis; UTI, urinary tract infection. From Giovannoni et al. 2022 with the permission of the authors [1].

How can we detect smouldering MS?

Professor Martina Absinta (Italy) gave a very clear summary of the emerging approaches to identify smouldering MS. Three promising imaging biomarkers can help identify the different, partially overlapping features of smouldering lesions. These are paramagnetic rim lesions (PRL), slowly expanding lesions (SEL) and translocator protein positron emission tomography (TSPO-PET) imaging.

The different features of the imaging biomarkers were presented by Professor Absinta. She explained that they represent a new window of opportunity for better visualising and monitoring of in vivo (micro)glial activity and chronic inflammation in MS. Professor Absinta emphasised that the imaging biomarkers have the potential to evaluate the efficacy of available disease-modifying therapies (DMTs) in treating chronic inflammation and in testing new treatments and new classes of agents that target glial activity. However, before these biomarkers can be used in routine clinical practice, further data are needed to inform guidance and education for neurologists and neuro-radiologists. Of interest, this is expected in the near future.

What is the role of ageing in smouldering MS?

The role of ageing mechanisms as key pathological drivers of smouldering MS processes was the focus of the presentation by Professor Antonio Scalfari (UK). Ageing processes in people lead to the progressive depletion of cognitive and brain reserve and the acceleration of brain atrophy. However, in MS, brain reserve is depleted more rapidly by the disease processes; thus, people with MS experience the impact of ageing earlier than people without the disease.

Professor Scalfari explained that although brain reserve can initially compensate for the effects of MS, this is lowered over time to a level at which it can no longer compensate. He stated that 'age-related neurodegeneration is an important pathological driver underpinning the clinical manifestation of smouldering MS'. Specifically, impaired and reduced remyelination causes axons to be more vulnerable to irreversible degeneration.

In addition, age-related iron accumulation within microglia is exacerbated in smouldering MS, leading to cellular damage. Iron also promotes the formation of reactive oxygen species and the release of pro-inflammatory cytokines, compounding the impact of MS disease processes. In closing, Professor Scalfari posited whether cellular senescence could become a target for neuroprotective treatments (senotherapy) in MS?

What does this mean for treatment decisions and holistic MS management?

Of key clinical interest are the potential therapeutic targets for smouldering MS. Are there DMTs available that could affect smouldering MS? Evidence suggests that certain DMTs that target B cells and CNS plasma cells and that promote remyelination could target pathological drivers of smouldering MS. These include cladribine, Bruton tyrosine kinase inhibitors and proteasome inhibitors. In addition, lifestyle changes (e.g. increased exercise, improved sleep hygiene, hormone replacement therapy, caloric restriction, intermittent fasting, ketogenic diets) and the prevention and treatment of certain comorbidities (e.g. cardiovascular dis-

ease, type 2 diabetes) could potentially have a direct benefit for people with MS. Further evidence is needed to fully elucidate the role of the various DMTs in the MS treatment armamentarium to effectively target smouldering MS.

An aim, and ongoing challenge, is to optimise the therapeutic management of MS for all patients with the early use of high-efficacy therapies to postpone, or at least reduce, smouldering pathology and slow MS progression. This would include patients who have progression without changes on conventional MRI.

In an impactful presentation, Ruth Stross (UK) emphasised the need to take a holistic management approach to improve outcomes for people with MS via a patient case study. Many patients with MS experience disease worsening that is under-recognised by many neurologists (e.g. disability progression, depression, cognitive decline), and the pivotal roles of anti-ageing and brain health are also undervalued, particularly given the impact of ageing mechanisms on smouldering disease processes.

Ms Stross, referring to the World Health Organization 2022 position paper, highlighted the importance of optimising brain health, which can 'not only reduce the prevalence and burden of neurological disorders but also improve mental and physical health overall'. Ruth explained that supporting patients' brain health and lifestyle management, in addition to bolstering their self-determination and MS self-management strategies, can be combined with therapeutic strategies to optimise MS management and improve patients' quality of life.

We were reassured that, at the end of the webinar, 96% of the attendees (compared with 78% at the start of the webinar) considered it extremely relevant for smouldering MS to be integrated into routine clinical practice. Half of the attendees will now always discuss smouldering MS with their patients as part of therapeutic decisions; this increased from 33%. As healthcare professionals, we need to educate ourselves on smouldering MS, given its importance and impact on the brain health and treatment of people with MS. We firmly believe that the future of MS treatment will be a combination of therapies and targeted brain health for better outcomes for patients.

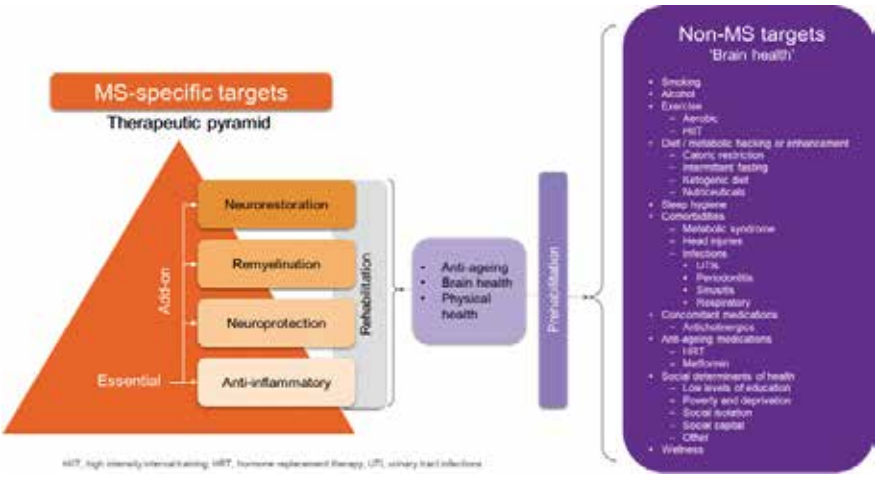

Figure 2. Combination therapy trials and the holistic management of MS. HIIT, high-intensity interval training; HRT, hormone replacement therapy; MS, multiple sclerosis; UTI, urinary tract infection. Adapted from Giovannoni et al. 2022 with the permission of the authors [1].

About triMS.online

triMS.online is a virtual, free-of-charge, not-for-profit event series open to all MS researchers and healthcare professionals. Pioneered in 2018 by Gavin Giovannoni and the not-for-profit company Oxford Health Policy Forum, triMS.online has the mission of connecting a diverse global audience and advancing equality for all working in the field of MS.

The series includes triMS.online conferences, triMSx webinars and triMSAudio podcasts.

The *triMSx* webinar 'Smouldering MS: what is it and how to approach it?' is available on demand in four languages; watch it at trimsonline-conference.com/smouldering-ms.

The seventh triMS.online conference is planned for 25 May 2023.

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