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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Tecfidera®
(dimethyl fumarate)

Let's say you're in your 20s or 30s... what does your daily life look like? Balancing work, family and social activities?

LOOK AT THE BIG PICTURE WHEN CHOOSING A DMT FOR YOUR RRMS PATIENTS

TECFIDERA is an established oral fumarate treatment[1] with efficacy demonstrated in newly diagnosed RRMS patients,[2] with **>562,000 patients having been treated worldwide to date**[1]*

Convenient oral treatment[3]

Taken as one pill with breakfast and a second with dinner[3†]

Elimination from the body in less than one day[3‡]

Provides flexibility, supporting treatment sequencing and patients' family planning decisions[3§]

* Of these, 6,413 patients (14,292 patient-years) were from clinical trials. Data cut-off 31st December 2021.[1]

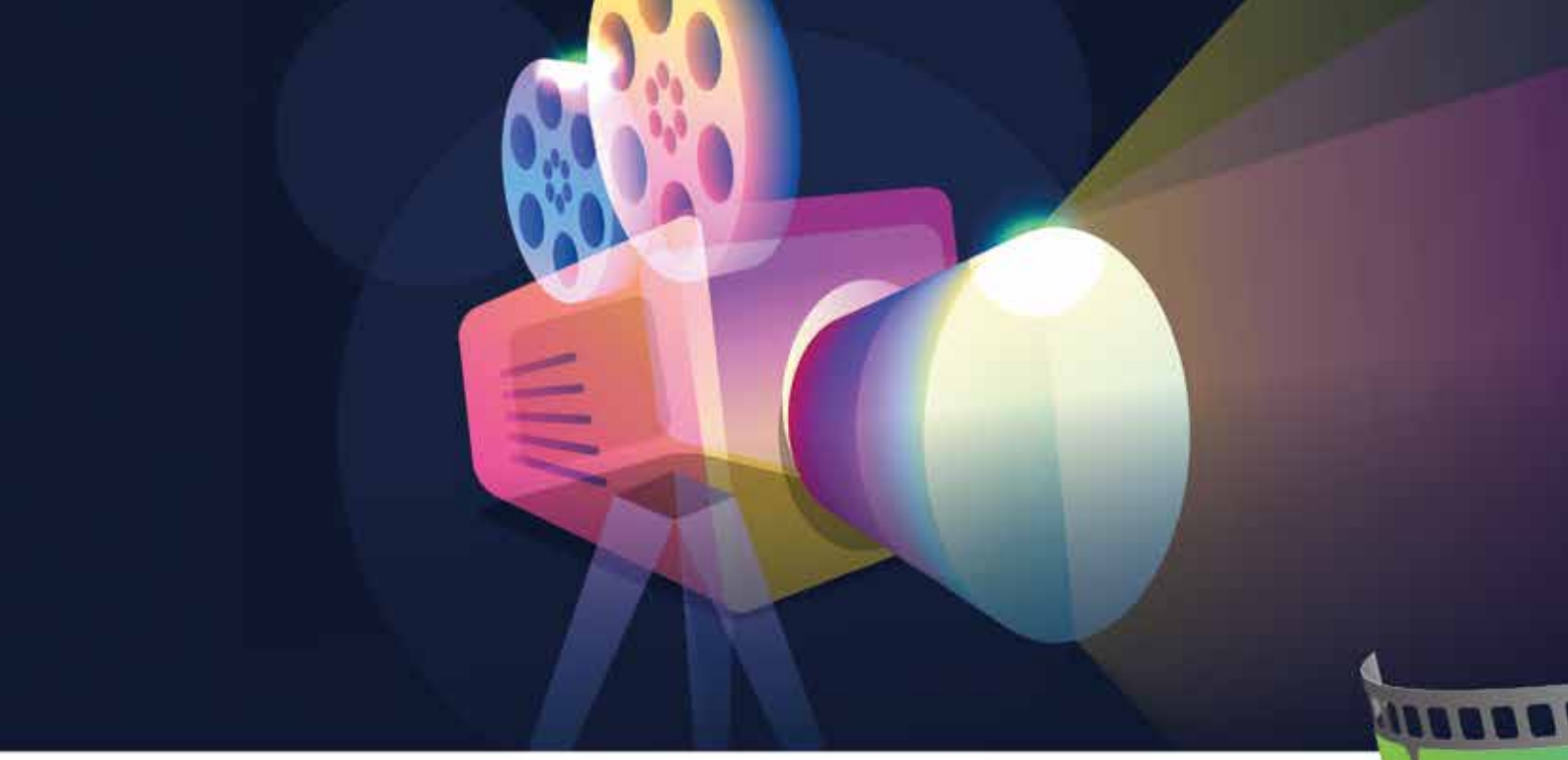
† **The starting dose is 120 mg twice a day. After 7 days, the dose should be increased to the recommended maintenance dose of 240 mg twice a day.**[2]

‡ The terminal half-life of monomethyl fumarate is short (approximately 1 hour) and no circulating monomethyl fumarate is present at 24 hours in the majority of individuals.[3]

§ **TECFIDERA is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception. TECFIDERA should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus.**[3]

Biogen-187337. Date of preparation: October 2022.

Biogen



Prescribing Information: Tecfidera® (dimethyl fumarate) 120 mg and 240 mg gastro-resistant hard capsules

Please refer to the Summary of Product Characteristics (SmPC) for further information. Indication(s): Treatment of adult patients with relapsing remitting multiple sclerosis (MS). **Dosage and administration**: Treatment should be initiated under the supervision of a physician experienced in the treatment of MS. Starting dose 120 mg twice a day, increased to recommended maintenance dose 240 mg twice a day after 7 days. Capsules must be swallowed whole and taken with food. Temporary dose reduction to 120 mg twice a day for up to one month may reduce flushing and gastrointestinal events. **Contraindications**: Hypersensitivity to dimethyl fumarate or to any of the excipients. Suspected or confirmed Progressive Multifocal Leukoencephalopathy (PML) **Special warnings and precautions**: PML has been reported in patients treated with Tecfidera. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in the setting of lymphopaenia. PML is caused by the JC virus (JCV) and may be fatal or result in severe disability. JCV testing has not been studied in Tecfidera-associated lymphopaenia. At first sign/symptom suggestive of PML, withhold Tecfidera and perform appropriate diagnostic evaluations (e.g. immediate MRI, determination of JCV DNA in CSF). If a patient develops PML, Tecfidera must be permanently discontinued. No studies have been performed evaluating use of Tecfidera when switching patients from disease modifying therapies (DMTs). PML cases have occurred in patients previously treated with natalizumab or prior immunomodulatory treatment. When switching from another DMT to Tecfidera, half-life and mode of action of prior therapy should be considered. Exercise caution in patients with pre-existing lymphopaenia. If lymphocyte count is low, alternative causes of lymphopaenia should be considered. Tecfidera may cause lymphopaenia, including severe and prolonged lymphopaenia. Tecfidera should not be initiated in patients with severe lymphopenia (lymphocyte counts < $0.5x10^9$/L). A current complete blood count, including lymphocytes, should be available prior to initiating treatment and must be repeated every 3 months. Discontinue therapy if lymphocyte counts < $0.5x10^9$/L persist for > 6 months. Evaluation of benefit/risk of continued therapy should be taken as the risk of an opportunistic infection (including PML) cannot be ruled out. If therapy is discontinued, lymphocyte counts should be followed until recovery and a decision to restart should be based on clinical judgement. Re-assess the benefit/risk in patients with lymphocyte counts ≥ $0.5x10^9$/L and < $0.8x10^9$/L for 6 months. In patients with lymphocyte counts below the lower limit of normal, regular monitoring of absolute lymphocyte counts is recommended. Baseline MRI should be available prior to treatment initiation. Further scanning should be considered as part of increased vigilance in patients considered at increased risk of PML. Changes in renal laboratory tests have been seen in trial subjects treated with Tecfidera. Renal function assessments are recommended prior to initiating treatment, after 3 and 6 months of treatment, every 6 to 12 months thereafter and as clinically indicated. Drug-induced liver injury, including liver enzyme (≥ 3 ULN) and total bilirubin (≥ 2 ULN) increases can result from treatment with Tecfidera. Assessment of serum aminotransferases and total bilirubin levels are recommended prior to initiation and during treatment as clinically indicated. Use with caution in patients with severe renal or hepatic impairment, or patients with severe active gastrointestinal disease. Prescribers and patients should be alert to the possibility of hypersensitivity or anaphylactoid reactions in the event of severe flushing reactions. Cases of anaphylaxis have been reported generally after the first dose. Treatment should be discontinued and patients should seek immediate medical care. Consider treatment suspension in the event of serious infection; reassess benefit/risk prior to resuming therapy. Cases of herpes zoster have occurred with Tecfidera including serious and non-serious cases and may occur at any time during treatment. Monitor patients taking Tecfidera for signs and symptoms of herpes zoster especially when concurrent lymphocytopenia is reported. If herpes zoster occurs, administer appropriate treatment. Consider withholding Tecfidera treatment in patients with serious infections until the infection has resolved. Treatment should be started gradually to reduce flushing and gastrointestinal adverse reactions. Cases of Fanconi syndrome have been reported with products containing fumaric acid esters. Early diagnosis of Fanconi syndrome and discontinuation of dimethyl fumarate treatment are important to prevent the onset of renal impairment and osteomalacia, as the syndrome is usually reversible. The most important signs are: proteinuria, glucosuria (with normal blood sugar levels), hyperaminoaciduria and phosphaturia (possibly concurrent with hypophosphatemia). Importantly, Fanconi syndrome can occur without elevated creatinine levels or low glomerular filtration rate. In case of unclear symptoms Fanconi syndrome should be considered and appropriate examinations should be performed. **Drug interactions**: Concomitant use of Tecfidera with a short course of IV corticosteroids was not associated with an increase in infection. IM interferon beta-1a, glatiramer acetate and oral acetylsalicylic acid did not alter the pharmacokinetic profile of dimethyl fumarate. Simultaneous use of other fumaric acid derivatives should be avoided during treatment with Tecfidera. Concurrent therapy with nephrotoxic medicines may increase the potential of renal adverse reactions in patients taking Tecfidera. **Pregnancy and lactation**: There are no or limited data from the use of dimethyl fumarate in pregnant women. Tecfidera is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception. It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk; a risk to newborns/infants cannot be excluded. The benefits of breastfeeding for the child and therapy for the woman should be considered when deciding whether or not to discontinue Tecfidera therapy. **Undesirable effects**: The most commonly (≥1/10) reported sides effects are flushing, diarrhoea, nausea, abdominal upper pain and abdominal pain and ketone measured in the urine. Other common side effects (≥1/100 to <1/10) include; gastroenteritis, lymphopenia, leucopenia, burning sensation, hot flushes, vomiting, dyspepsia, gastritis, gastrointestinal disorder, aspartate aminotransferase and alanine aminotransferase increase, pruritus, rash, erythema, alopecia proteinuria, feeling hot, albumin urine present and white blood cell count decrease. See special warnings and precautions for other serious side effects. See SmPC for full list of side effects. **Legal classification**: POM. **Pack size and basic NHS price**: 120 mg capsules x 14 £343.00; 240 mg capsules x 56 £1373.00. **Marketing Authorisation numbers**: Ireland/Northern Ireland: EU/1/13/837/001-002; Great Britain: PLGB 22407/0012, PLGB 22401/0013. **Marketing Authorisation Holder**: Biogen Netherlands B.V., Prins Mauritslaan 13, 1171 LP Badhoevedorp, The Netherlands. **Date of last revision of Prescribing Information**: January 2022.

Adverse events should be reported.
For Ireland, reporting forms and information can be found at www.hpra.ie.
For the UK, reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store. Adverse events should also be reported to Biogen Idec on medinfouki@biogen.com 1800 812 719 in Ireland and 0800 008 7401 in the UK.

TECFIDERA is indicated for the treatment of adult patients with RRMS.[3]

The most common AEs (occurring in ≥10% of patients cumulatively) included flushing, diarrhoea, nausea, abdominal pain upper, abdominal pain and ketones measured in urine. Common AEs (occurring in ≥1 to <10% of patients cumulatively) included gastroenteritis, lymphopenia, leukopenia, burning sensation, hot flush, vomiting, dyspepsia, gastritis, gastrointestinal disorder, aspartate aminotransferase increased, alanine aminotransferase increased, pruritus, rash, erythema, alopecia, proteinuria, feeling hot, albumin urine present and white blood cell count decreased. Please refer to the SmPC for further information.[3]

Abbreviations: AE: Adverse Event; **DMT**: Disease-Modifying Therapy; **RRMS:** Relapsing-Remitting Multiple Sclerosis.

References: 1. Biogen, data on file, TEC028. **2.** Gold R, et al. Mult Scler. 2015;21(1):57-66. **3.** Tecfidera SmPC.

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Our front cover features a self-portrait drawn by 13-year-old Willow which is part of the Tourettes Action Creativity Awards (TACA) Exhibition launched by the National charity Tourettes Action.

This online gallery is the first of its kind and is the result of a Summer event encouraging young people with TS to get creative across a range of disciplines.

The exhibition is a unique curation of original art and performance pieces from talented young people living with this often misunderstood neurological condition.

For more information visit www.tourettes-action.org.uk

In Memoriam: Donna Earl

I'd like to apologise to our contributors and advertisers for the late publication of this issue. Many of you already know that our designer and friend Donna Earl passed away suddenly at the end of August.

Donna was a lynchpin of the ACNR team for 22 years – she created the original design and has produced article layouts and advertisements for many of you in that time.

We're a small, tight-knit team and as you can imagine this has been a challenging time. We're grateful for your understanding.

Rachael Hansford, ACNR Publisher

Todd Hardy, Co-Editor.

This issue is emblematic of ACNR's distinctive dedication to publishing a broad range of articles of neurological interest to engage both the subspecialist and non-subspecialist reader.

In the first article, Shane Lyons, Sean O'Dowd, Richard Walsh and Tim Lynch from Dublin cast their eyes up and down the latest advances in progressive supranuclear palsy (PSP). Of interest, is that the authors recommend a trial of co-enzyme Q10 for patients affected with PSP as it may improve gait in some patients.

The Headache series, edited by Anish Bahra, sees Anne MacGregor from London discuss the important topic of migraine in perimenopausal women. Changes in the hormonal milieu are likely to be the trigger for these headaches and transdermal oestrogen at biological doses, as opposed to synthetic oestrogen, can assist with management.

The very modern neurological problem of functional tic disorders induced by phenomena such as social media and the COVID-19 pandemic is addressed by Neil Ramsey and Vicky Marshall from Glasgow and Jon Stone from Edinburgh.

JMS Pearce from Hull introduces us to Solomonovna Stern, a Latvian doctor and physiologist from the early 20th century who made seminal contributions to our understanding of the blood-brain-barrier and who was persecuted by Stalin during her time as the head of physiology at the Second Moscow State University.

Our case report by Adam Boardman from Liverpool and co-authors is a rare description of symptomatic CSF hydrothorax complicating thoracotomy for thoracic disc protrusion.

The conference reports are from Viva Lee reviewing the MS Academy Basecamp 3, Amy Ross Russell who attended EAN 2022, Richard Cole who attended BNPA 2022 and Angelika Zarkali who reviewed the 2022 International Lewy Body Disease Conference.

Our book reviews are from Orlagh Jones reviewing "Pharmacology Case Studies for Nurse Prescribers" by Donna Sholefield and Nicole Blichtlau who reviews "Neurotrauma and Critical Care of the Brain" by Jack Jallo and Christopher M. Loftus.

We hope you enjoy this edition of ACNR.

Todd Hardy, Co-Editor
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A list of our full editorial board can be found at www.acnr.co.uk/about-acnr/editorial-board/

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Progressive supranuclear palsy in 2022: recent developments and an eye to the future

Abstract

Progressive supranuclear palsy (PSP) is an uncommon, progressive, neurodegenerative condition which classically presents with eye movement abnormalities, axial rigidity, early falls and cognitive impairment. The range of recognised phenotypes associated with PSP has expanded significantly in recent years. Imaging markers can assist in the diagnosis of PSP, while novel imaging modalities and laboratory-based biomarkers offer hope for earlier and more accurate diagnosis. While no disease modifying treatments are yet available, several therapies may be useful in ameliorating symptoms. Despite disappointing recent clinical trial results, several agents are currently under investigation for the treatment of PSP.

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative condition associated with the proliferation of 4-repeat (4R) tau through the brain. Clinically, the condition is characterised by axial rigidity, oculomotor abnormalities, and cognitive impairment with prominent postural instability and early falls. Recent revisions to diagnostic criteria and treatment guidelines have altered our understanding of PSP. While no disease modifying treatment is currently available, a range of promising therapies are under investigation.

Epidemiology and aetiology of PSP

The mean age of onset is 66.4 years (SD +/-12) years [1] and progresses to death over an average 6-7 years, although some subtypes follow a slower course and a substantial proportion (up to 24% in one study) survive for longer than 10 years [2,3]. Estimates of PSP prevalence vary considerably with rates of 5-6 per 100,000 commonly quoted, although a recent study of Yonago City, Japan reported a prevalence as high as 17.9 per 100,000 [4, 5]. Estimates of the annual incidence of PSP range from 0.9-1.9 per 100,000 [6,7]. Data from the UK Biobank, a large prospective cohort study of more than 500,000 people, has been used to study potential pre-diagnostic features of PSP. In this study, 176 people who subsequently developed PSP showed differences in reaction time, hand grip strength, fluid intelligence, prospective memory and tendency to fall compared to controls, with reaction time the strongest predictive marker (8).

PSP is typically a sporadic disorder, however, familial cases related to mutations in the MAPT gene as well as cases related to LRRK2 mutations have been identified [9,10]. While genome wide association studies (GWAS) have identified several risk loci for PSP [11]. In addition GWAS studies have identified variations in LRRK2 influencing survival in PSP, in particular the rs2242367 allele [12]. Studies of geographical clusters of PSP have helped to identify several environmental risk factors. A PSP-like parkinsonian syndrome identified in Guadeloupe has been associated with the consumption of annonaceae fruit which contain annonacin, mitochondrial complex I inhibitor, which has been shown to increase 4R tau isoforms in cultured neurons [13,14]. Hypertension, lower levels of education, and rural living are some of the other potential risk factors which have been investigated [15].

Pathologically, PSP is characterised by microtubule-associated protein tau aggregates composed of tau isoforms with four microtubule-binding repeats (4R-tau). These aggregates are in the form of neurofibrillary tangles, oligodendrocytic coils, and astrocytic tufts [16,17]. It is hypothesised that in PSP aberrant tau spreads throughout the brain in a prion-like fashion (spreading hypothesis). Typically the brainstem and basal ganglia are involved early in the disease course with evidence of rostral (particularly the frontal lobes) and caudal (dentate nucleus and cerebellum)

spread in more advanced cases [18]. This topographical pattern varies and underlies the different clinical phenotypes of PSP seen by the clinician early in the disease.

Clinical presentation

The single most common presentation of PSP consists of axial rigidity, oculomotor abnormalities, and cognitive impairment, as described by Richardson, Steele, and Olszewski in their 1964 paper which first drew attention to PSP as a distinct clinicopathological entity [19]. This presentation, which became known as Richardson's Syndrome (RS), is the most commonly recognised form of PSP. The motor syndrome is often accompanied by cognitive impairment of a frontal-dysexecutive type with reduced speed of processing, apathy, and impulsivity [20]. Language is frequently impaired with reduced fluency. Features of language peculiar to PSP include letter fluency more impaired than category fluency [21], a tendency to generate low frequency words [22] and a particular impairment for action naming words [23]. Sleep disturbance is common in PSP with patients frequently describing difficulty initiating and maintaining sleep, and demonstrating abnormal sleep architecture [24].

The NINDS-PSP diagnostic criteria, published in 1996, were heavily influenced by the classic RS phenotype. These criteria have been shown to have good specificity for PSP pathology [25]. However, the phenotypic spectrum of PSP is much broader than that initially described, a fact which limits the sensitivity of these criteria [26-28]. These presentations are generally less specific for PSP pathology than PSP-RS. In 2017, the Movement Disorders Society published updated criteria for the diagnosis of PSP [27]. These criteria provide several levels of diagnostic certainty with presentations of "definite", "probable", "possible" PSP, and "suggestive of" PSP. The criteria recognised characteristic impairments in four domains: oculomotor function, akinesis, postural instability, and cognitive function with specific syndromes of impairment being considered more characteristic, and therefore more suggestive, of a diagnosis of PSP (for example, within the akinesia domain, progressive freezing of gait is considered more compelling evidence of PSP than akinetic-rigid, predominantly axial parkinsonism, which in turn is more characteristic than Parkinsonism with tremor, asymmetry, or levodopa responsiveness) [28]. These clinical features, in varying combinations, are used to define eight PSP clinical subtypes (Table 1) [29,30]. A number of additional supportive clinical features are recognised including early dysphagia, hypokinetic and spastic dysarthria (the characteristic "dysarthrophonia" of PSP), photophobia, and levodopa-resistance (where levodopa-responsiveness occurs in PSP it is seldom sustained). The akinetic syndrome seen in PSP may consist of hypokinesis without decrement, a finding which may help to distinguish PSP from PD [31].

The establishment of consensus clinical criteria for PSP subtypes may provide more precise information on the natural history of PSP subtypes. One large study, which included 101 cases of PSP, found distinctive patterns of progression, cognitive impairment, and serological markers for subgroups of presentation [32]. Despite the dramatic increase in the range of presentations recognised by the MDS criteria, some reported PSP phenotypes, such as PSP with predominant cerebellar ataxia (a proposed PSP-C) remain without formal diagnostic criteria [33].

Table 1. Clinical phenotypes according to the 2017 Movement Disorders Society Criteria

Subtype	Abbrev.	Clinical features for probable/possible diagnosis
PSP with Richardson's Syndrome	PSP-RS	Probable: Vertical supranuclear gaze palsy or slow vertical saccades and repeated unprovoked falls within 3 years or falling on pull-test within 3 years. Possible: Slow vertical saccades and more than two steps on pull test within 3 years.
PSP with progressive gait freezing	PSP-PGF	Probable: Vertical supranuclear gaze palsy or slow vertical saccades and progressive gait freezing within 3 years. Possible: Progressive gait freezing within 3 years.
PSP with predominant parkinsonism	PSP-P	Probable: Vertical supranuclear gaze palsy or slow vertical saccades and parkinsonism with tremor/asymmetry/levodopa response.
PSP with predominant frontal presentation	PSP-F	Probable: Vertical supranuclear gaze palsy or slow vertical saccades and frontal cognitive/behavioural presentation.
PSP with predominant oculomotor dysfunction	PSP-OM	Possible: Vertical supranuclear gaze palsy.
PSP with predominant postural instability	PSP-PI	Possible: Repeated unprovoked falls within 3 years or falling on pull test within 3 years.
PSP with predominant CBS	PSP-CBS	Possible: Vertical supranuclear gaze palsy or slow vertical saccades and corticobasal syndrome.
PSP with predominant speech/language disorder	PSP-SL	Possible: Vertical supranuclear gaze palsy or slow vertical saccades and nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech

Adapted from Höglinger et al. Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria. Mov Disord. 2017 Jun;32(6):853-864 [27].

Ancillary investigations

Changes on structural imaging of the brain can support a clinical diagnosis of PSP. Brainstem atrophy, particularly affecting the midbrain, can be seen on MRI. The "hummingbird" [34] and "morning glory" [35] signs, on midsagittal and axial images respectively, are seen in PSP, but lack sensitivity. Hypointensity seen within the putamen in T2 imaging, which is associated with ferritin deposition in pathological studies, can distinguish PSP from PD with reasonable specificity (91%, 95%CI 80-96%) but limited sensitivity (69%, 33-90%) [36]. The magnetic resonance parkinsonism index (MRPI) is calculated by multiplying the pons area-midbrain area ratio (P/M) by middle cerebellar peduncle (MCP) width-superior cerebellar peduncle (SCP) width ratio (MCP/SCP) helps to identify cases of parkinsonism likely to evolve to PSP [37]. A subsequent refinement of this measurement, which includes a measurement of third ventricle width has been shown to improve upon the sensitivity of the MRPI (98.1% vs 73.5%) while preserving specificity [38]. FDG-PET imaging reveals decreased glucose metabolism in the midbrain early in the disease course while decreased metabolic activity in the caudate, putamen, and prefrontal cortex occur later [39]. PET imaging using tau-specific ligands to image tau deposition in a range of neurodegenerative disease has been the subject of investigation for over a decade. First generation tau ligands,such as [18F]-flortaucipir [40], have been used in many research studies but their utility was limited by off-target binding (e.g. to monoamine oxidase B (MAO-B) in the basal ganglia) resulting in an overlap in tracer binding between different diagnostic groups [41]. Second generation ligands (e.g. [18F] MK-6240)[42]have been developed which demonstrate increased specificity, without off target binding to MAO-B which may improve the diagnostic utility of tau-PET imaging.

Treatment

A range of strategies are used to ameliorate symptoms and improve quality of life in PSP. In 2021, a consensus statement on the management of PSP was published by the CurePSP Centres of Care Network which is a useful guide to current best practice in the symptomatic management of PSP [43].

The involvement of a multidisciplinary team with experience in neurodegenerative disease is essential. Physiotherapy, focused on maintaining strength, balance, aerobics, and coordination is helpful.The selection of walking aids requires some consideration as walking sticks prevent falls in only one direction and may constitute a tripping hazard. Weighted walkers, some of which are designed to prevent the backwards falls which predominate in PSP, are preferred. In cases of severely restricted mobility wheelchairs equipped with a tilt-in-space mechanism to prevent falls and facilitate optimal positioning for swallowing are useful. Adaptations to the home as well as other functional adaptations require the input of a skilled occupational therapist. Speech therapy support in the accurate assessment and management of dysphagia and dysarthria is invaluable. Communication difficulties can be reduced with the use of alphabet boards and text-to-speech systems. The early involvement of a Palliative Care service can be extremely helpful especially with regard to the need for hospice care as well as the management of multiple complex symptoms. Patients should consider appointing an enduring power of attorney early in the disease course to avoid difficulties which may arise should cognitive impairment become problematic. Patient support groups can provide peer support to people with PSP and their families.

Important pharmacological options to consider include:

- Levodopa may help with bradykinesia, rigidity, and tremor. 20-30% of patients with PSP respond to levodopa. A target dose of 800-1200mg per day is usually recommended.
- Amantadine, titrated to a maximum dose of 100mg tds may be helpful for gait dysfunction but may produce deleterious cognitive effects, livedo reticularis, ankle/leg swelling, or postural hypotension.
- Liposomal coenzyme Q10 (100mg tds) provides a benefit to gait in a small proportion of patients and a trial is recommended.
- Benzodiazepines may be helpful for dystonia.
- Melatonin can be useful for insomnia.
- Cholinesterase inhibitors should be used only where there are pronounced amnestic deficits and otherwise are best avoided.
- Botulinum toxin can be used in the treatment of focal dystonia and for apraxia of eyelid opening.

No disease modifying treatment for PSP currently exists but a number of different agents utilising a range of pharmacological mechanisms are under investigation. Disappointingly, 2021 saw negative results for two Phase 2 trials of anti-tau monoclonal antibodies directed against the extracellular N-terminal tau: the PASSPORT (gosuranemab) and ARISE (tilavonemab) trials [44, 45]. These agents target free extracellular tau in an attempt to disrupt the spread of aberrant tau from cell to cell and have previously shown promise in mouse and primate models but failed to demonstrate clinical benefit over 52 weeks, despite a reduction in free extracellular tau in CSF in the active arm.

There are a number of possible reasons for the lack of demonstrable benefit of immunotherapy targeting extracellular tau in PSP. In the first instance, participants were recruited on the basis of a PSP-RS presentation. While this presentation is reasonably specific for tau pathology, phenotype-pathology correspondence is not perfect and non-PSP mimics have been reported, study cohorts including heterogenous pathology will attenuate treatment effects of pathology specific therapies [30]. PSP-RS phenotypes correspond to widespread pathology and may represent a more advanced stage of the disease when extracelluar tau-reducing therapies have limited use. Therapies to date have targeted the N-terminal of extracellular tau, which may not be mediator of proposed tau-related toxicity [46,47]. Finally, it is possible that the aggregation of tau may represent the consequence of an alternative disease-causing process rather than being pathogenic in itself, in which case removal of these markers of disease would have a limited impact on disease progression [48].

Given the influence of LRRK2 on survival in PSP, there is significant interest in treatments targeting LRRK2 in idiopathic Parkinson's disease including LRRK2 kinase inhibitors and antisense oligonucleotides targeting LRRK2 [49]. Further studies involving an array of agents are ongoing, including tolfenamic acid, a NSAID which inhibits the tau transcription factor Sp1 [50], selenium selenate, monoclonal antibodies targeting alternative binding sites on the tau protein (UCB0107) [51], agents which modify mitochondrial function (MP201) or lipid peroxidation (RT001) [52] and antisense oligonucleotides to reduce the production of tau (NIO752) [53].

A persistent challenge in neurodegenerative disease, including PSP, is that presenting symptoms are often non-specific and relate to the early topographical pathological distribution and hence the diagnosis may be delayed. As a result, by the time a definitive diagnosis is made pathological changes are widespread and disability established such that prospects of effective treatment are diminished. The search for early and reliable biomarkers, clinically-, imaging- or CSF-based, or serum or skin or wearable device data or big data analysis may allow early identification of cases and initiation of treatment at an earlier stage.

Conclusion

PSP is a complex,progressive,neurodegenerative condition which has an enormous impact on the daily functioning, quality of life, and social circumstances of patients and their families. Patients commonly present with axial rigidity, gaze abnormalities, and cognitive impairment, although a wide range of phenotypes are described. Although no disease modifying treatment exists, a range of strategies may help manage the symptoms and complications of the condition while multiple agents which may modify the disease process are under evaluation.

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Cerebrospinal fluid hydrothorax in a rehabilitation medicine patient following thoracotomy for thoracic disc protrusion

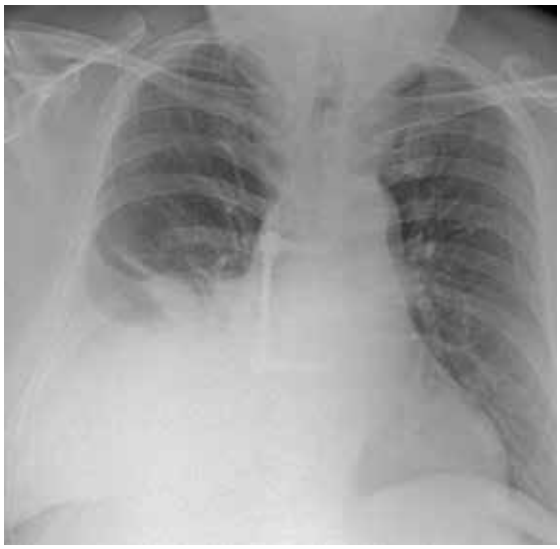
Abstract

Cerebrospinal fluid (CSF) hydrothorax has been reported most commonly as a complication of ventriculo-pleural/-peritoneal shunt insertion, but also due to duro-pleural fistula. Here we report a case of CSF hydrothorax in a rehabilitation patient due to duro-pleural fistula following thoracotomy for thoracic myelopathy secondary to disc protrusion. This case highlights the need for high clinical suspicion following thoracotomy, and urgent specialist input from the neurosurgical team.

A 58-year-old male with a history of chronic back pain suffered severe pain to his mid thoracic back after heavy lifting. After 10 days his symptoms progressed to include bilateral lower limb weakness, neuropathic pain in his right foot, and paraesthesia around his umbilicus. He also reported that his bowels had been more 'sluggish' and he had difficulty passing urine. He presented to his local A&E, and was found to have T7/8 disc protrusion with cord compression and early myelopathy, in addition to L4/5 severe spinal canal stenosis and generalised degenerative changes.

The patient was transferred to the regional neurosurgical specialist centre and underwent right sided anterior thoracotomy for resection of T7/8 disc protrusion. Trench vertebrectomy was performed. A large area of calcified ossification of the posterior longitudinal ligament (OPLL) was found, with adherent dura at the level of calcification. OPLL was dissected and resected into the vertebrectomy defect and the cord was decompressed. As the OPLL was adherent to the dura, this dissection resulted in dural tear. Rib was used for vertebrectomy fusion. The dura was reconstructed with dural patch and tisseel glue, and a right anterolateral plate and screws were used for fixation from T6-T9. Further surgical intervention was planned in future for the lumbosacral canal stenosis. Post-operatively he developed headache and neck ache felt to be due to cerebrospinal fluid (CSF) leak, and had bilateral lower limb weakness in keeping with spinal cord injury. CT brain confirmed collapse of the ventricular system, but the patient was neurologically stable and no further intervention was felt to be indicated by the neurosurgical team.

Once stable post-operatively, he was transferred to the regional spinal cord injury centre for ongoing rehabilitation. On admission it was noted that his headache was still ongoing since the operation, and after 4 days he became unwell with suspected chest infection. Examination revealed reduced air entry in the right lower lobe, and chest X-ray (CXR) showed patchy shadowing in that region. He completed a course of antibiotics, then after a further 2 weeks he deteriorated again with shortness of breath on exertion. Chest X-ray demonstrated a moderate right-sided pleural effusion, and this was confirmed by CT. He was reviewed by the respiratory team, and a therapeutic aspiration was performed. 1900mls of light straw-coloured fluid was obtained and sent for biochemistry, culture and sensitivity, and cytology. Biochemistry showed a borderline exudate, but otherwise investigations were unremarkable. A CXR after the aspiration showed a moderate pleural effusion still remained, so a repeat therapeutic aspiration was performed 1 week after the first. 2000mls of straw-coloured fluid was aspirated, and



Chest X-ray showing large right sided cerebrospinal fluid hydrothorax, with visible metalwork from T7/8 reconstruction

investigations showed a similar picture as previously. The team was concerned that he had no obvious reason for a typical cause of effusion – there were no signs of heart failure and B-type natriuretic peptide was normal, there was no evidence of a renal or liver cause, and no evidence of an underlying cause for exudative effusion. Due to the intra-operative dural tear, suspicion of CSF leak post-operatively, and ongoing headache, we felt that the effusion could be CSF. We were unsure whether this could result in such a large effusion without causing more significant neurological symptoms. We contacted the laboratory to test his CSF for beta-trace protein (BTP); the biochemist was initially reluctant due to the chance of a false negative when performing the test on pleural fluid, but agreed because there was a high clinical suspicion. This was reported as showing BTP 15.6mg/L, suggesting the fluid was in fact likely CSF.

We contacted the neurosurgical team who arranged urgent transfer back under their care. MRI imaging showed kinking and high signal within the cord at the level of the recent surgery, with the cord being anteriorly positioned within the thecal sac. Lumbar drain insertion was initially difficult due to the patient's degenerative spinal disease, so lumbar decompression was performed, and a drain inserted under direct vision. The patient then developed signs of re-accumulation of fluid, and CXR confirmed a larger pleural effusion. He was transferred to intensive care for chest drain insertion, and 2000mls was drained. Initially the plan was to monitor with a lumbar drain in-situ to allow time for spontaneous closure of the fistula. However, due to ongoing fluid accumulation despite conservative measures, he was taken to theatre for definitive surgical closure. Following successful treatment, he returned to our care to continue rehabilitation.

Discussion

Patients with thoracic disc herniation often present late as thoracic nerves have no limb motor control. Thoracic radiculopathy typically presents with neuropathic pain across the chest, which can be misdiagnosed as shingles or pain of a muscular/cardiac/abdominal cause. In more advanced stages of disc herniation myelopathy can develop. The majority of patients with thoracic myelopathy simply have back pain alone prior to developing ataxia and lower limb weakness, discoordination and sensory deficit.

The choroid plexus produces around 400 – 600mls of CSF per day, whilst the healthy pleural cavity can reabsorb up to around 200mls of fluid per day [1]. If there is a significant CSF leak into the pleural space, an effusion can develop relatively quickly. Inflammation can decrease the ability of the pleural space to reabsorb fluid, and further expedite the accumulation of fluid.

Routine pleural fluid investigations tend to show a clear/straw coloured transudate, but are not diagnostic for CSF. BTP is made in the choroid plexus within the ventricles of the brain, and is found in the central nervous system in much higher concentrations than elsewhere in the body. When at diagnostic levels, BTP is highly specific and sensitive for the diagnosis of CSF. When testing pleural fluid there is a risk of CSF being diluted by the presence of other fluid, thus giving a false negative result. BTP is generally tested for when there is a high suspicion of CSF leak, rather than as part of routine investigations. Similarly, beta-2-transferrin can also be used for diagnosis.

Most reported cases of CSF hydrothorax are secondary to ventriculo-pleural/-peritoneal shunt complications [2-5]. Other reports describe duro-pleural fistula as seen in this case, most commonly when both the dural and pleural membranes are disrupted [1,6,7]. Clinicians should have a high index of suspicion with effusions following thoracic spinal surgery, where anterolateral thoracotomy is the standard approach [7]. Negative pressure within the pleural space causes a pressure gradient, allowing fluid to pass into the pleural cavity. Draining can cause the pressure gradient to increase, resulting in more CSF entering the pleural cavity [1,7]. This can lower the CNS pressure and put the patient at risk of developing intracranial hypotension that can lead to subdural hygromas, subdural haemorrhage or brain herniation [1]. Furthermore, chest drain insertion poses a significant risk of CNS infection [7]. Spontaneous resolution is rare, and in most cases surgical closure of the fistula is required [6,8]. In conclusion, high clinical suspicion of CSF hydrothorax in these patients should be prompted by the surgical approach, and history of post operative postural headache, dyspnoea, cough or respiratory distress. A thorough respiratory clinical evaluation is necessary, along with CXR and specialised tests such as beta 2 transferrin. Neurosurgical input for specialist advice should be sought without delay.

Key Points

1. Thoracic disc prolapse may present as radiculopathy typically with neuropathic pain across the chest, but motor deficit can be seen in more advanced stages when myelopathy develops secondary to cord compression.
2. The choroid plexus produces 400-600mls of cerebrospinal fluid per day whilst the healthy pleural cavity can reabsorb around 200mls per day, meaning a CSF effusion can develop relatively quickly.
3. Testing for beta-trace protein is highly specific and sensitive in detecting CSF.
4. Draining a CSF effusion can increase the pressure gradient, allowing more fluid to enter the pleural cavity, and risking brain herniation.

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Great Britain Prescribing Information: Kesimpta® ▼ (ofatumumab)

Important note: Before prescribing Kesimpta 20 mg solution for injection in pre-filled pen consult Summary of Product Characteristics (SmPC).

Presentation: Solution for injection in pre-filled pen. Each pre-filled pen contains 20 mg ofatumumab in 0.4 ml solution (50 mg/ml). Ofatumumab is a fully human monoclonal antibody produced in a murine cell line (NS0) by recombinant DNA technology.

Indication(s): Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

Dosage and administration: Treatment should be initiated by a physician experienced in the management of neurological conditions and the first injection should be performed under the guidance of an appropriately trained healthcare professional. The product is intended for patient self-administration by subcutaneous injection. The recommended dose is 20 mg ofatumumab with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4. *Paediatric population:* The safety and efficacy of ofatumumab in children aged 0 to 18 years have not yet been established.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Patients in a severely immunocompromised state. Severe active infection until resolution. Known active malignancy.

Warnings/Precautions: *Injection-related reactions:* Patients should be informed that injection-related reactions (systemic) could occur, generally within 24 hours and predominantly following the first injection. From clinical studies the most frequently reported symptoms include fever, headache, myalgia, chills and fatigue. Injection-related reactions can be managed with symptomatic treatment, use of premedication is not required. Injection site reaction (local) symptoms observed in clinical studies included erythema, swelling, itching and pain. *Infections:* It is recommended to evaluate the patient's immune status prior to initiating therapy. Based on its mode of action and available clinical experience, ofatumumab has the potential for an increased risk of infections. Administration should be delayed in patients with an active infection until the infection is resolved. Since John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML) has been observed in patients treated with anti-CD20 antibodies, other MS therapies, and ofatumumab at substantially higher doses in oncology indications, physicians should be vigilant for medical history of PML and for any clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, treatment with ofatumumab should be suspended until PML has been excluded. Hepatitis B reactivation has occurred in patients treated with anti-CD20 antibodies. Patients with active hepatitis B disease should not be treated with ofatumumab. HBV screening should be performed in all patients before initiation of treatment. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment. Patients in a severely immunocompromised state must not be treated until the condition resolves. It is not recommended to use other immunosuppressants concomitantly with ofatumumab except corticosteroids for symptomatic treatment of relapses. *Vaccinations:* All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of ofatumumab for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ofatumumab for inactivated vaccines. Ofatumumab may interfere with the effectiveness of inactivated vaccines. The safety of immunisation with live or live-attenuated vaccines following ofatumumab therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion. In infants of mothers treated with ofatumumab during pregnancy live or live-attenuated vaccines should not be administered before the recovery of B-cell counts has been confirmed. Depletion of B cells in these infants may increase the risks from live or live-attenuated vaccines. Inactivated vaccines may be administered as indicated prior to recovery from B-cell depletion.

Interactions: No interaction studies have been performed, as no interactions are expected via cytochrome P450 enzymes, other metabolising enzymes or transporters. The response to vaccination could be impaired when B cells are depleted. The risk of additive immune system effects should be considered when co-administering immunosuppressive therapies with ofatumumab.

Fertility, pregnancy and lactation: Women of childbearing potential should use effective contraception while receiving ofatumumab and for 6 months after the last product administration. There is a limited amount of data from the use of ofatumumab in pregnant women. Treatment with ofatumumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. The use of ofatumumab in women during lactation has not been studied. It is unknown whether ofatumumab is excreted in human milk. There are no data on the effect of ofatumumab on human fertility.

Undesirable effects: Very common (≥1/10): upper respiratory tract infections, urinary tract infections, injection-site reactions (local), Injection-related reactions (systemic). Common (≥1/100 to <1/10): oral herpes, blood immunoglobulin M decreased.

Legal classification: POM

Marketing Authorisation (MA) number, quantities and price: PLGB 00101/1201 - unit pack of Kesimpta 20 mg solution for injection in pre-filled pen containing 1 pre-filled pen: £1,492.50.

Date of last revision of prescribing information: April 2021

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

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Headache series - Introduction

The Headache Series aims to address topical issues in headache. Despite being the most common neurological disorder, management remains challenging. This series was introduced by the topic of vestibular migraine, in which it is often not the headache but the neurological symptoms which confer the brunt of the disability. Forthcoming editions include the association with sex hormones, well known but less well understood and the advent of the new anti-CGRP monoclonal antibody treatments.

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Migraine in perimenopausal women

By E. Anne MacGregor, MB, BS, MSc, MD, FFSRH

Abstract

There is an unmet need for effective diagnosis and management of migraine in perimenopausal women. Menstrual cycle hormone disruption during perimenopause is associated with an increase in migraine and menstrual migraine prevalence, together with other more commonly recognised menopause symptoms. Women of perimenopause age, i.e., early 40s to mid 50s, should routinely be asked about migraine and menopause symptoms, and provided with effective tools for management as appropriate. Simple diaries can be used to identify the frequency and duration of attacks, as well as the relationship to menstruation at outset, and to monitor response to treatment. While there is no evidence to support prescription of hormone replacement therapy (HRT) solely for management of migraine, it is the most commonly used treatment for menopause symptoms. As some types and regimens of HRT can negatively affect migraine, the general recommendation is to use transdermal oestrogen and continuous progestogen regimens where possible. In contrast to contraceptive synthetic oestrogens, physiological doses of natural oestrogen can be used by women with migraine aura. Most women, particularly those with a history of menstrual migraine, can be reassured that the natural history of migraine is to improve with increasing years post menopause.

Introduction

Perimenopause typically begins when a woman is in her early to mid-40s. It is the stage of hormonal transition from previously regular, predictable menstrual cycles that encompasses dynamic changes with the hypothalamic-pituitary-ovarian axis, culminating in menopause. Menopause transition is marked by disrupted menstrual cycles as hormone production from the ovarian follicles becomes erratic, with high estradiol levels and low luteal phase progesterone [1]. This results in symptoms of irregular bleeding, hot flushes, night sweats, mood changes and sleep disturbance that are characteristic of this stage of life. Natural menopause is defined as having occurred after 12 months of amenorrhoea following the last menstrual period. In the UK, average age at natural menopause is 51 years but ranges between 45 and 55 years. Although ovulation ceases at menopause, ovarian hormonal activity persists for several years post menopause, as reflected by a gradual decline in symptoms.

The prevalence of migraine, and menstrual migraine in particular, increases during the menopause transition and improves with increasing time following physiological menopause, mirroring changes in the hormone environment [2].

This paper discusses the clinical management of migraine during perimenopause and the role of HRT.

Epidemiology

Migraine is an under-reported complaint in perimenopausal women and is both underdiagnosed and undertreated in this population. In a recent study of women attending a London menopause clinic, 41% were diagnosed with migraine, of whom 27% experienced attacks of migraine with aura [3]. Using the validated Headache Impact Test (HIT-6), migraine associated disability was very severe (HIT-6 60+) or substantial (HIT-6 ≥56≤59) in 48% of migraineurs. Despite this high level of disability, most women were treating attacks with paracetamol alone, or had been prescribed medication containing codeine, which is inappropriate for migraine management [4].

In contrast to the benefits of physiological menopause, hysterectomy with or without oophorectomy is associated with a higher prevalence of migraine compared to women who have not had surgery [5].

Menstrual migraine

During perimenopause some women report regular perimenstrual attacks of migraine. As shown in Table 1, the International Headache Society defines menstrual migraine as migraine attacks that occur within a 5-day window starting two days before the first day of menstruation, through to the third day of bleeding [6]. Solely perimenstrual attacks (pure menstrual migraine) are uncommon and most women also experience attacks at other times of the cycle (menstrually related migraine). In women diagnosed with menstrually related migraine, perimenstrual attacks are more severe, more disabling, last

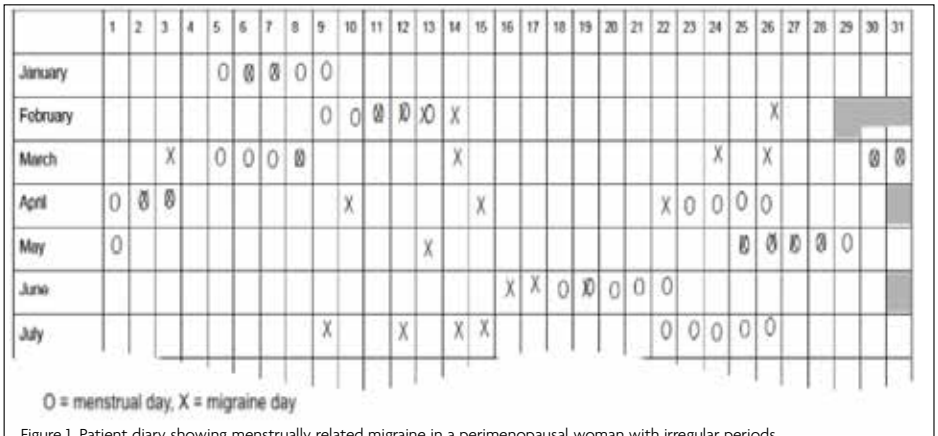

Figure 1 Patient diary showing menstrually related migraine in a perimenopausal woman with irregular periods

Table 1: Diagnostic criteria for menstrual migraine without aura (pure menstrual migraine and menstrually related migraine) proposed by the Third International Classification of Headache Disorders (ICHD-3), 2018

Menstrually related migraine without aura
A: Attacks, in a menstruating woman, fulfilling criteria for migraine without aura B: Attacks occur on day 1±2 (i.e, days -2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle
Pure menstrual migraine without aura
A: Attacks, in a menstruating woman, fulfilling criteria for migraine without aura B: Attacks occur exclusively on day 1±2 (i.e, days -2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle
Note: The first day of menstruation is day 1 and the preceding day is day -1; there is no day 0. For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy

longer and are less responsive to symptomatic medication compared with attacks at other times of the cycle [7]. These perimenstrual attacks are typically without aura, even in women who have attacks with aura at other times of the cycle. To confirm a genuine hormonal relationship, a diagnosis of 'menstrual migraine' should only be made if the association between perimenstrual attacks and menstruation is greater than chance [7].

A diagnosis of menstrual migraine is aided by use of simple diaries with pictorial representation of migraine attacks and menstruation on each day of the month, as show in Figure 1. This diary confirms the diagnosis of menstrually related migraine, in which menstruation is irregular but associated with regular perimenstrual attacks, that are of longer duration compared to attacks at other time of the cycle.

Pathophysiology

Studies have not identified any consistent biochemical or hormonal abnormalities in women with perimenopausal migraine, compared with control groups. It is likely that a number of independent mechanisms act perimenstrually, which can occur discretely or in combination. One established mechanism for menstrual attacks of migraine is the natural fall in oestrogen during the late luteal phase of the normal menstrual cycle [7]. A likely reason why this is a relevant factor during perimenopause is the significantly higher perimenstrual estrogen levels in perimenopausal compared to premenopausal women [8].

High estrogen levels during perimenopause also increase the risk of menorrhagia, [9] which is accompanied by an increase in prostaglandins and prostaglandin metabolites in the systemic circulation [10]. Infusion of prostaglandins has been shown to induce migraine like attacks, so increased prostaglandin release during perimenopause is a likely additional risk factor for migraine [11].

Progesterone is metabolised to allopregnanolone, a potent positive allosteric modulator of GABA-A receptors, inhibiting cortical excitability [12]. Thus, the increase in anovulatory cycles and consequent low luteal phase progesterone levels that characterise perimenopause may further increase the risk of migraine at this time.

Management

Migraine must first be diagnosed before it can be optimally managed. Given the association between migraine and perimenopausal vasomotor symptoms, women seeking help for menopause should be asked about migraine symptoms and vice versa [13].

Lifestyle

Lifestyle changes, including sleep hygiene, regular exercise, regular meals, and maintaining a healthy weight benefit both migraine and menopause symptoms.

Management of acute attacks

Symptomatic treatment should be provided in accordance with local or national guidelines [4, 14]. Diaries can be used to assess the frequency of medication as regular use more than 2-3 days a week risks medication overuse headache.

Prophylaxis

Migraine prophylaxis should be considered if migraine attacks are frequent and/or symptomatic treatment does not provide effective attack control. Unless a diagnosis of menstrual migraine is made, standard migraine prophylaxis is indicated, in accordance with local or national guidelines [4, 14].

Women diagnosed with menstrual migraine have the option to try specific targeted evidence-based perimenstrual or continuous prophylaxis, including contraceptive hormonal regimens, as shown in Table 2. Data regarding the effects of other contraceptive methods on migraine are limited. Depot medroxyprogesterone acetate inhibits ovulation and the menstrual cycle and so should be effective on potential mechanisms for perimenstrual exacerbation of headache [15]. The progestogen-only implant inhibits ovulation but does not reliably inhibit ovarian activity. Although some women using the implant experience fewer migraine attacks, particularly those who become amenorrhoeic, this method more often results in fluctuating estrogen levels, unscheduled bleeding, and exacerbation of migraine. To date, there are no data regarding the effect of the drospirenone progestogen-only pill on migraine.

Hormone replacement therapy

Hormone replacement is indicated for management of typical perimenopausal symptoms and not specifically for migraine management. It should be prescribed in accordance with local or national guidelines [16, 17]. However, some types and regimen of HRT can negatively affect migraine and inappropriate use of HRT during early perimenopause can augment hormone fluctuations, further exacerbating migraine. To maximise benefit to migraine, the aim is to maintain stable hormone levels where possible (Table 3). If migraine persists once other menopause symptoms are controlled, review non-hormonal triggers and consider non-hormonal management strategies (Table 4).

In contrast to use of contraceptive synthetic oestrogens women with migraine aura can use HRT. Transdermal oestrogen should be prescribed where possible as it does not adversely affect risk of ischaemic stroke [18]. If a woman develops new onset confirmed migraine aura when starting HRT, switch to transdermal if not already prescribed, reduce the oestrogen dose, or consider non-hormonal options.

Conclusion

Migraine is adversely affected by hormone changes during the menopause transition. Healthcare providers treating perimenopausal women should specifically ask about migraine symptoms, diagnosing and treating accordingly. Where HRT is indicated, continuous regimens with transdermal oestrogen are least likely to adversely affect migraine and, by stabilising hormone levels, may benefit migraine.

Table 2: Specific prophylaxis for menstrual attacks of migraine in women diagnosed with menstrual migraine

Perimenstrual prophylaxis				
NSAIDS	Mefenamic acid	500mg three times daily	Start 2–3 days before the expected onset of menstruation and continue for the first 2–3 days of bleeding If periods are irregular start on the first day of bleeding First-line agents for migraine attacks that start on the first to third day of bleeding, particularly in the presence of dysmenorrhoea and/or menorrhagia	Side effects of NSAIDs include gastrointestinal disturbance Contraindications include peptic ulcer and aspirin-induced allergy Interactions include anticoagulants and antihypertensive agents If NSAIDs are effective, consider the 52mg levonorgestrel intrauterine system which has similar benefits to mefenamic acid and also provides contraception
	Naproxen	500mg once or twice daily		
Triptans	Frovatriptan	Take 5mg frovatriptan twice daily on first day then continue frovatriptan 2.5mg twice daily for a further 5 days	Start two days before expected onset of menstrual attack of migraine	
Continuous hormonal prophylaxis				
Combined hormonal contraception	Continuous regimen (no break) or flexible extended regimen (take a 4-day break following four or more days of troublesome bleeding)		Contraindicated for contraceptive use in women with migraine aura Combined oral contraceptives containing levonorgestrel or norethisterone preferred for women over 40 due to the potentially lower VTE risk compared to other progestogens Not recommended for contraceptive use in women over age 50 Can provide menopause symptom management Topiramate may reduce contraceptive efficacy	
Desogestrel progestogen only pill	Continuous regimen		Unscheduled bleeding common side effect Can be used in conjunction with HRT – note contraceptive dose does not provided adequate endometrial protection Topiramate may reduce contraceptive efficacy	

Table 3: Hormone replacement therapy for women with migraine

Oestrogen
● Transdermal oestrogen recommended – gel daily, patches once or twice weekly, spray daily
● Initiate oestrogen using low doses and increase gradually until non-migraine menopause symptoms controlled
Progestogen
● Use a continuous regimen rather than cyclical where possible
● Use non-oral synthetic progestogens e.g., transdermal norethisterone or levonorgestrel intrauterine system
● Oral micronized progesterone is converted to allopregnanolone, with potential benefit to migraine

Table 4: Non-hormonal prescription medication that can benefit migraine and vasomotor symptoms

Drug class	Drug name	Dose / day	Comments
SSRIs	Escitalopram	10-20 mg	Unlicensed Better tolerated than venlafaxine
	Paroxetine	20-40 mg	Unlicensed Better tolerated than venlafaxine Avoid concomitant use with tamoxifen
SNRIs	Venlafaxine	37.5-150 mg	Unlicensed More evidence of efficacy for migraine
Alpha-adrenergic agonist	Clonidine	50-150 mcg	Licensed for migraine prophylaxis and menopause flushing Antihypertensive

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Functional tics, the pandemic and social media

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Abstract
Functional tics form a part, albeit a small proportion, of the wider spectrum of functional neurological disorders (FND). In this review, we focus on the recent increase in presentations of functional tics since the COVID-19 pandemic. A functional tic disorder is often characterised by rapid onset of complex motor and vocal tics predominantly in adolescent females, distinct from Tourettes syndrome which typically begins in younger boys. Rapid onset of severe tics merging into other types of functional neurological disorders, marked coprolalia, self-injury from tics and school absenteeism, are additional features of functional tics, however, the disorders can co-exist. There has been a lot of focus on social media as an explanation for the rise in cases, although the data suggest that this is just one of many potential factors, with the pandemic itself and its effect on teenage lives being the most likely culprit.

Tics are abnormal sudden, rapid and repetitive movements or vocalisations [1]. Tics can occur as simple vocal/motor tics, as part of Tourette syndrome, as a functional tic disorder (as a subtype of functional neurological disorder) or rarely other neurological conditions. Unlike simple tic disorder, Tourette syndrome requires the presence of both vocal and motor tics lasting for at least 1 year [2] from onset in childhood.

An increase in patients with a functional tic disorder

Tic disorders have been described for centuries with Tourette syndrome characterised in the late 19th century [2]. Functional tics have been described in the context of "hysteria" as early as 1902 [3], but historically have been relatively rare making up 1-5% of new referrals to specialist tic disorder clinics [4], and with only three case series prior to 2019 [5].

Since early 2020 there has been a rise in functional tics, gathering significant attention within the media and literature (see Figure 1) [6]. These typically have affected adolescent females and have been especially noticed by specialist tic clinics. Referrals have risen typically from 1-2% to 20-35% in locations as disparate as Calgary, Sydney, London, and Los Angeles [4].

Differentiating between Tourette syndrome and functional tics

Table 1 summarises some key differences, although clinicians should always consider the possibility of dual diagnosis. The onset of symptoms is a vital discriminator. Tourette syndrome has an average age of onset of 6 years [7] with a significant male predominance. Tics typically start insidiously in contrast with functional tics where there is often a rapid onset typically in late adolescence, and more commonly in females [4].

Tics in Tourette syndrome are initially subtle with intermittent simple motor movements typically in the face that come and go such as repetitive blinking, facial grimacing or sniffing. In comparison, simple tics such as sniffing are relatively absent in functional tics. There is then often a progression to more complex and persistent motor tics in a rostral-caudal pattern from face to arm [7]. This usually develops into more complex multifocal tics involving vocalisation in adolescence, often improving by early adulthood. Tourette syndrome tics are usually preceded by an initial sensory "urge," an unpleasant sensation usually in the area of the tic, however, it's important to recognise that most patients with Tourette's will experience a number of tics without urge (particularly simple tics of the face). The motor or vocal tic often occurs in response to this urge and allows temporary relief. Tourette syndrome tics are not considered completely involuntary as they are normally suppressible to a degree, although the act of suppressing can be unpleasant and associated with rebound worsening.

In functional tics [5] arm movements appear to predominate, in contrast to facial tics in Tourette syndrome. Complex tics and coprolalia appear early, in comparison to Tourette syndrome where these would only occur years after the onset of simple tics. Although people with functional tics do sometimes describe urge and suppressibility, this is less common than in Tourette syndrome. Coprolalia, copropraxia and self-injurious behaviour are rare in Tourette syndrome but occur in up to 50% of patients with functional tics [8]. Functional tics have been noted to commonly lead to significant disability [5], which may involve emergency admission to hospital as well interfering with school or work, again less common with Tourette syndrome.

An important feature to consider is prolonged tics or "tic attacks", where tics become continuous and sometimes violent. Such episodes are less common in Tourette syndrome as compared to functional tics. These episodes share similar features of hyperkinetic attacks with retained awareness seen in FND that might also be called functional seizures. Functional tics are commonly seen alongside FND, and sometimes functional tics can improve when other FND symptoms worsen, in keeping with functional tics having a different mechanism to Tourette syndrome. It is important to note, however, that people with Tourette syndrome also describe a worsening of tics when "behind closed doors," such as at home or in a car. This is often a "release" after the effortful suppression of tics in front of others, which can also commonly be called a "tic attack" [9]. This highlights the importance of understanding the phenomenology of a patient's tic symptoms, with any "tic attack" presentation contextualised alongside the natural history of their tics.

Clinical examination can prove a challenge in discriminating between Tourette syndrome and functional tics, in marked contrast to the differentiation of other functional movement disorders. Features that are useful in differentiating other functional movement disorders such as variability, distractibility and suggestibility are not reliable tests as tics in Tourette syndrome may also have these qualities [5]. Co-occurrence with other functional neurological symptoms is suggestive. Neurophysiological testing may not help either as motor readiness potentials (Bereitschaftspotential) can be present in both, although precede Tourette syndrome tics less commonly [10].

Co-morbid psychiatric pathology is often present in both conditions. Tourette syndrome is a complex neuropsychiatric syndrome commonly associated with OCD and ADHD. Differences exist in those obsessive behaviours seen in Tourette syndrome (in comparison to primary OCD). Obsessions with symmetry, calculation and the "just right" phenomenon are commonplace in Tourette Syndrome but not in functional tics. The presence of anxiety and depression is common to both disorders and is therefore a poor discriminator [11,12].

Evidence for social media influence and the pandemic in the rise of functional tic disorder presentation

In a study before the pandemic, a cohort of patients presented separately with a similar phenomenology of tic disorders to those shared on a well-known YouTube channel [13]. These videos showed complex vocalisations that had been informally attributed to Tourette syndrome, but were more in keeping with functional tics, with patients reporting sudden onset of similar behaviours [13]. This study, however, only selected patients who admitted to exposure to social media, with little focus on other predisposing factors. It should be noted that people with Tourette syndrome do report worsening tics when watching others with tics (echopraxia), as well as sometimes experiencing an influence on the content of vocal tics from others (echolalia).

Figure 1: Recent articles from the media and journal articles highlighting growing interest in functional tics

Table 1: Clinical features differentiating between Tourette syndrome and functional tics

	Tourette syndrome	Functional tics
Peak age of onset	4-6 years	Mid-teens
Gender predominance	Male	Female
Tempo of onset	Insidious onset from childhood, peaking at 10-12 then improving	Rapid onset in late adolescence/ early adulthood
Simple tic history	Usually present	Rare but watch out for dual diagnosis
Bodily distribution	Usually facial at onset spreading caudally	More commonly arms and trunk
Prolonged tics	Rare	Common
Premonitory Urge	Common, although can be absent in simpler tics	Uncommon, although physiological arousal symptoms may occur which are relieved by the tic
Ability to Suppress tics	Present	Present in some patients
Interference with other voluntary actions	Rare	Common
Variability in direction and number of different behaviours	Rare	Common
Self-injurious behaviour from tics (e.g. head banging, body punching, biting)	Less frequent	Common
Injury to others from tics	Rare	Common
Presence of other functional symptoms or disorders including FND	Rare	Common

In a larger study, some centres reported exposure to social media in all their patients, but this was not the case in each centre, highlighting that the link is not absolute [4]. A recent study found that only 18% of 22 patients with functional tics (taken from 185 referrals to their tic clinic over this period) had social media exposure [12].

Social media probably has played a role in the increase of patients with functional tics. The popularity of TikTok has increased significantly since the pandemic with 5.8 billion views of videos with keywords such as #tourette and #tic in March 2021 alone [8]. However, an increase in viewership does not simply infer causality. The individual social media content of tic-like behaviours can be consumed by millions of viewers, however, only a tiny number of patients develop functional tics.

A more nuanced hypothesis has been proposed [12] in which the influence of social media is viewed as playing a part in a wider picture of neuropsychiatric vulnerability. The pandemic and its associated social isolation have involved significant social stressors, especially for teenagers, including issues with academic achievement, domestic confinement, and worsening mental health. These factors

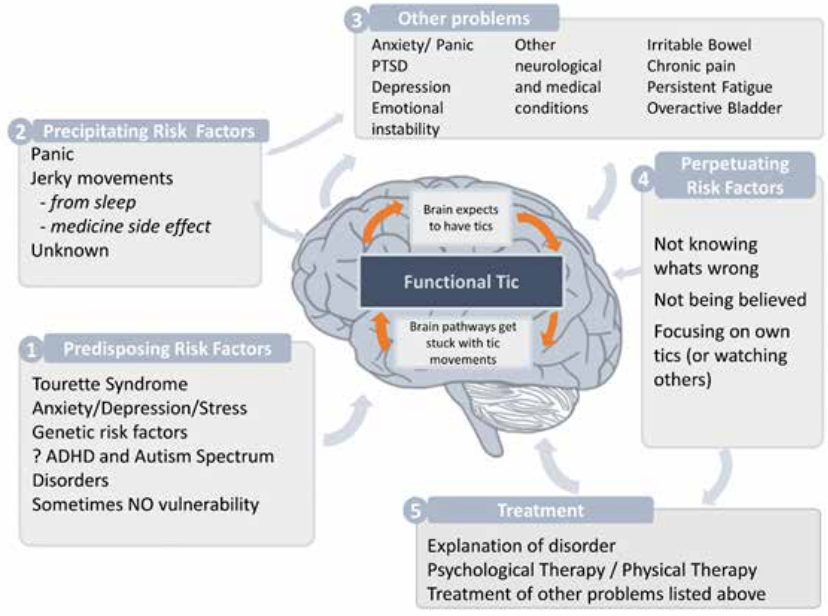

Figure 1: A multifactorial model of mechanism and aetiology for functional tics.

could all promote maladaptive habitual movement pathways in the brain, emotional dysregulation, and FND, including tics (Figure 2).

Therefore, with functional tics, and like any patient with FND, having a wider view of the patient and their social setting is key, rather than a more simplistic focus on social media and catchy headlines such as "TikTok Tics". Overemphasis on social media runs the risk of inadvertently blaming individual patients for "catching" their symptoms through viewing habits. In addition, many patients with Tourette syndrome report an increased stigma towards them as people incorrectly assume that their disorder is also a result of too much social media use.

Management of functional tics

In Tourette syndrome, symptoms tend to improve in late adolescence with cognitive behavioural intervention therapy (CBiT). This includes habit reversal training as a firstline intervention [2]. Medications that are sometimes prescribed in Tourette syndromes, such as clonidine or antidopaminergic drugs such as risperidone or tetrabenazine, should not be used for people with functional tics, highlighting the importance of an accurate diagnosis.

There is little data on the prognosis and treatment of functional tic disorder, but early reports of the outcome, especially in younger teenagers, are encouraging. Like any other form of FND, a clear explanation from a clinician is vital as a platform for being able to engage with and access multidisciplinary treatments. Cognitive behavioural therapy may include strategies to help divert abnormally focused attention away from tics, CBiT may have a role in the management of functional tics. This shares many features with current approaches to physiotherapy and some types of psychological therapy for functional movement disorder. It also seems reasonable to suggest limiting time looking at others with tics in case that is exacerbating it. Treatment of other comorbidities such as anxiety and depression, if present, and liaising with schools and employers to restore more normal activities are also important [10,14].

Conclusion

A functional tic disorder is a distinct subtype of FND that can be associated with marked disability and distress. Differentiating functional tics from Tourette syndrome, and recognising when they may co-exist, has important implications for prognosis and treatment. The increase in cases seen globally may in part relate to exposure to social media use, but the phrase "TikTok Tics" hugely oversimplifies a clinical issue that affects young people who have experienced pressures on physical and mental health during the COVID-19 pandemic.

Resources

- There is a functional tic self-help sheet written by some of the leading experts on tics at: www.neurosymptoms.org/en_GB/symptoms/fnd-symptoms/functional-tics/
- www.tourettes-action.org.uk: Has useful support information on Tourette syndrome
- The American Academy of Neurology hosted a podcast on this topic: https://directory.libsyn.com/episode/index/id/21928034

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Prolonged use of benzodiazepines may result in dependence with withdrawal symptoms on cessation of use. *Suicidal behaviour:* Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients with a history of depression and/or suicide attempts should be kept under close supervision. *Concomitant use with alcohol / CNS depressants:* The concomitant use of clonazepam with alcohol or/and CNS depressants should be avoided. Such use has the potential to increase the clinical effects of clonazepam possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression. 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Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. Abrupt withdrawal of the drug should therefore be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose. The risk of withdrawal symptoms is increased when benzodiazepines are used with *day-time sedatives. Lactose intolerance:* Clonazepam tablets contain lactose and should not be taken by patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption. *Porphyria:* Clonazepam should be used with care in patients with porphyria. *Paediatric population:* In infants and small children clonazepam may cause increased production of saliva and bronchial secretion. Therefore special attention must be paid to maintaining patency of the airways. **For further information please refer to SmPC. 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Particularly in long-term or high-dose treatment, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced coordination of movements and gait disorder (ataxia) and nystagmus may occur. Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. Other adverse effects include diplopia, cardiac failure (including cardiac arrest), salivary or bronchial hypersecretion with drooling in infants and small children. **Refer to SmPC for full details. Legal category:** POM. **Presentation & cost:** 100 x 0.5 mg tablets £32.27; 100 x 1 mg tablets £41.95; 100 x 2 mg tablets £34.99. **Marketing authorisation holder and numbers:** Neuraxpharm UK Limited, Unit 12, Farnborough Business Centre, Eelmoor Road, Farnborough GU14 7XA, UK. (0.5 mg) PL 49718/0060, (1 mg) PL 49718/0061 and (2 mg) PL 49718/0062. **Date of revision of text:** August 2022.

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MS Academy Basecamp 3

Conference details: 7-8 July, 2022. Halifax Hall, Sheffield, UK ***Report by:*** Viva Levee, National Hospital of Neurology and Neurosurgery, Queen Square, London, UK
Conflict of interest statement: None declared.

This was a course organised by the Multiple Sclerosis (MS) Academy, held over 2 days at the Halifax Hall in Sheffield. The course was conceptualised by neurologist Dr Riffat Tanveer who had undertaken research which showed that trainee neurologists largely feel unsupported in developing skills in the specialist area of MS. In response, there has been the creation of a MasterClass series to provide innovative, supportive and up to date courses to enhance trainee skills in MS. This was the third Basecamp course that was aimed at junior doctors in the earlier years of their neurology career journey, specifically doctors in the pre-registrar level. The course provided an invaluable resource of knowledge of the very common condition of MS as well as an opportunity to show evidence of commitment to neurology in preparation for registrar interview applications.

Prior to the course attendees were given comprehensive programmes as well as reading material which was very useful.

The layout of the conference room and the structure of lectures allowed for relaxed yet thought provoking discussion throughout. The lectures were interactive and informative, and the speakers were very engaging.

The first day of lectures included two lecture sessions held by MS neurology consultants based in Sheffield.

Day 1

Session 1

Dr Azza Ismail led the first session which was highly comprehensive. She spoke of the details of the diagnostic process of MS, including the application of the Macdonald Criteria, importance of history and examination and also the consideration of atypical presentations and taking care not to miss the 'MS mimics'. She spoke of key clinical phenotypes and the red flags. She emphasised points through clinical cases which was very useful and relevant. Going through cases illustrated the difficulties that can arise in the diagnosis and also the decision for treatment. She also spoke of how to determine when and what treatment, including eligibility for disease modifying treatment and the process of "de-risking" DMTs.

Session 2

The second lecture session was led by Dr Riffat Tanveer. This focused on how to confirm the diagnosis of MS and how to communicate this to a patient. The session was very useful to critique our own practice, and think about practicalities such as how to word clinic letters and the importance of including enough relevant information, as well as the need to digest the investigations and previous letters yourself prior to having a potentially life changing conversation with a patient – there is a need to "convince yourself" also.

He spoke of counselling required once the diagnosis of MS is confirmed, including pregnancy and family-planning. Dr Tanveer also went through the classification of MS – in terms of active vs highly active, and how this impacts the treatment choice. He also spoke of prognostic tools which can be used to guide treatment as well as the maintenance escalation vs. immune reconstitution treatment strategies and how we might explain this to our patients.

Day 2

Session 1

The first session was lead by Consultant Neurologist Dr Rhian Raftopoulos, from King's College in London. She spoke of the important components of an MS clinic – including how to record notes and construct letters, as well as the key aspects of MS care to focus on. This included a holistic approach to MS care – addressing the various symptoms that can arise, including cognitive difficulties, bladder and bowel incontinence as well as the very common symptom of fatigue.

She went into more detail about "MS bladder issues" and the way to approach this, with conservative and medical/interventional means. She also spoke of fatigue in MS and the multidisciplinary approach to addressing this – involving therapists, neuropsychologists etc. This session really honed in on the importance of taking time to go through each symptom and trying to "unpick" what was really happening – how to try to tease out if a patient might be progressing, or if they might be having a relapse vs a pseudo-relapse, and importantly prompting the patient to highlight if they needed more support or attention to a specific symptom or concern.

Session 2

This session was lead by the Consultant Neurologist Dr Kate Petheram who works in Sunderland where she is lead of the MS service. Her session focused on how to have difficult conversations with patients regarding explaining the cause of their MS. She spoke of the genetic vs environmental causes, and modifiable risk factors. She also spoke of the incidence of MS in families and how this is increased compared to risk in the general public.

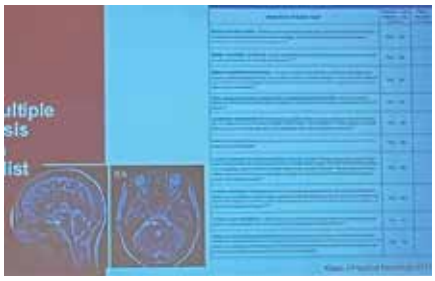
During the session she discussed the vast and expanding range of disease modifying therapies and also of the use of stem cells in MS which provides a promising new opportunity for improving patients' long term outcomes and reduction in disability. She also discussed the current trials and importantly of the eligibility criteria and where to access more information to educate our patients.

Session 3

Session 3 was a case based series led by Consultant Neurologist Dr David Paling, who practices in Sheffield and is the Strategic Director of the MS academy.

He went through four fascinating cases, each with different important learning points.

When discussing the cases he highlighted the need to take a detailed history and to prompt patients to discuss their symptoms, and importantly to highlight any change in their level of function as this could be a sign of disease progression. He also spoke of a case where there was physical decline which did not correlate with new lesions or radiological activity and the decisions regarding changing treatment vs continuing on efficacious therapy. He mentioned tumefactive MS, and how these cases often present as stroke calls and then respond to immunosuppression in the form of steroids in the acute phase. Dr Paling then spoke of the decisions involved in whether to start these patients on disease modifying therapy and the evidence behind this.



In summary

Each speaker was very engaging, passionate and evidently at a high level of expertise about their field of MS. This was inspiring for junior trainees like myself, and I feel like I have gained a good knowledge base which I aim to continue to expand on. This knowledge will benefit me both in my general medicine as well as in my neurology placements and future registrar years. I really enjoyed the course, and I found the MS Academy team to be professional yet friendly, efficient, and very well organised. I will definitely attend future courses and continue to engage with the MS community and use the learning resources in my clinical practice.

European Academy of Neurology Conference – EAN 2022

Conference details: 25-28 June, 2022. Vienna, Austria ***Report by:*** Amy Ross Russell, NIHR Clinical Research Fellow, Neurology Trainee, Southampton, UK.
Conflict of interest statement: None declared.

The 8th Conference of the European Academy of Neurology took place in Vienna this summer, amidst scorching temperatures and glorious sunshine.

As warm a welcome (although a much more comfortable temperature) was waiting inside the Austria Centre, which was a fantastic venue- well laid out, and easy to negotiate, with good spaces for working, networking, and plentiful refreshments from attentive staff.

The conference was officially opened by Professors Claudio Bassetti and Tony Marson who welcomed the phenomenal Baroness Susan Greenfield to the stage. Her opening address: "Where Neuroscience meets neurology: blowing, expanding, and losing the mind" was itself mind-blowing – a discussion of the neuroscience behind consciousness and control, simultaneously scientifically rigorous and philosophically questioning. She used models of neurodevelopment to help listeners understand her pioneering work in neurodegeneration, and discussed her current research in Alzheimer's disease, the role of acetylcholinesterase, and whether peptide analogues of related small molecules may have therapeutic benefit.

Other stand-out lectures for me included the Moritz Romberg lecture, given by Professor Bo Norrving, who spoke about stroke systems and systematics, and the Camillo Golgi lecture, given by Hans Lassman, who spoke on the contribution of neuropathology to our understanding of multiple sclerosis.

Professor Norrving reminded us of the global burden of stroke and the need for action, talking through systematic gaps and opportunities for improvement, how services can be implemented, and took us through the reclassification of stroke as a neurological illness in the ICD-11. It was a heartfelt, sincere, inspiring talk and felt particularly timely for UK delegates as we embrace stroke within the new neurology curriculum.

Professor Lassman talked through the extra dimensions that pathology can give to our understanding of a disease. He explained the differences between multiple sclerosis and MOG-antibody disease through pathological observations, and what this tells us in terms of location of pathology, timing of disease activity, immune system dynamics and the underlying pathological substrate.

Other headline speakers were Professor Kailash Bhatia, who gave the Brown-Sequard lecture on "The translational clinician: big gains from small observations", using case examples to remind us of the importance of deep clinical phenotyping and the Brain Prize lecture, given by Michael Moskowitz, who spoke on "The trigeminovascular system as a template for discovery in migraine."

Amongst these headlines there was a wealth of other offerings. From case-based workshops to focused symposia, e-posters in a quiet, removed area, and career development sessions. The wide range of topics spanned the entire neurology curriculum, and there really was something for everyone, whatever your area of interest, or level of experience. There was a fantastic offering for students and trainees with lots of case-based workshops and teaching sessions. I particularly enjoyed the clinical grand round session, led by Patrick Altman and supported by neuroradiology and pathology colleagues, with detailed discussion of three excellent, complex cases and the differential diagnoses that had been considered along the way.

I was also delighted to attend the session focusing on challenges for women in neurology, where three inspirational speakers gave an account of their journey through neuroscience, identifying challenges they had faced, approaches they had used to overcome these, and offering heartfelt advice for women facing similar obstacles. This addition to the programme felt like an important step in ensuring equal opportunities in neurology and although there is a long way to go, I felt encouraged that we are approaching an era when diversity of all kinds is being celebrated, and flexibility in working patterns and training pathways considered, if not yet encouraged. Identifying challenges allows us to discuss priorities and current problems. Discussing together how we can create equal opportunities is the first step to providing these, and these sessions are a fantastic initiative from the EAN. Thank you.

It was an absolute delight to be able to attend in person, share space and ideas over excellent coffee, and be surrounded by the buzz of a conference again. In addition to this, the conference was hybrid, meaning those unable to attend in person could attend remotely, and allowing all delegates the opportunity to re-watch sessions, or view simultaneous sessions on "catch-up". This logistical feat feels like a positive step and sets the bar high for delivering a highly flexible, inclusive, and all-encompassing conference. I would highly recommend further involvement with the EAN to UK colleagues, who were relatively underrepresented amongst the delegates. In addition to a comprehensive, diverse conference, with opportunities for neurologists of all stages and interests, there are a multitude of educational, quality improvement and career development opportunities. Visit www.EAN.org for more information.

BNPA 2022 Annual Conference

Conference details: 26-27 May, 2022, Royal College of Physicians, Regents Park, London, UK. ***Report by:*** Richard Cole, BNPA committee psychiatry trainee representative. ***Conflict of interest statement:*** Richard Cole is a member of the BNPA committee.

This year's 35th BNPA Annual Conference took place on the 26th and 27th May, our first in-person meeting since 2019. It was held in the Royal College of Physicians' iconic building on Regent's Park, described as a 'modernist masterpiece'.

Hundreds of neurologists, psychiatrists and psychologists journeyed in, brightened by the sun, whilst many more joined virtually.

Along with our usual BNPA Medal Award and JNNP Plenary Lecture, this year's themes included:

- Medicolegal aspects of neuropsychiatry
- Inflammation
- Neuromodulation
- Neuropsychiatry of Interoception

Day 1 started with the very entertaining BNPA medal lecture on Neuropsychiatry Mavericks by Professor Anthony David, a BNPA former chair and founding member, and Director of the UCL Institute of Mental Health. Professor David guided us through a 150-year history of neuropsychiatry mavericks. Along the way he highlighted the key characteristics common to the maverick's personality type and explored the significance in the modern age.

Then Dr Christopher Bass opened the session on Medicolegal aspects of neuropsychiatry. He highlighted the behavioural spectrum that falls under the controversial and often misused term "malingering." Within this context, Dr Bass covered the challenges of revealing the degree of symptom exaggeration/amplification in mild Traumatic Brain Injury (mTBI) and Functional Neurological Disorder (FND). He focused on the importance of establishing a chronology from multiple sources, but also on the importance of an awareness of the iatrogenic contribution to symptom perpetuation.

Professor Alan Carson then spoke about FND in the context of personal injury, covering diagnosis, symptom exaggeration, onset, risk and triggers and treatment, and described his approach in helping the court decide on the sequence of events and where might lie the blame.

After refreshments, Dr Virginia Newcombe, Consultant in Neurosciences and Trauma Critical Care Medicine, and Emergency Medicine, challenged common beliefs about TBI and delved into the world of post-concussion symptoms. Dr Newcombe enlightened us on what's new in mTBI, highlighting the importance of pre-injury factors in symptom development, as well as describing how common post-concussion symptoms (e.g. headache, dizziness and fatigue) are in the general population.

At midday Dr Quinton Deeley, Consultant Psychiatrist and Senior Lecturer in Social Behaviour and Neurodevelopment (and with a previous BA in Theology and Religious Studies) gave a thought-provoking talk about free-will and criminal responsibility. He explored both philosophical and neuropsychiatric insights in the control of behaviour; how these can be impaired and the implications for notions of criminal responsibility.

A memorable example was a case of kleptomania after frontal lobe injury, where the patient was aware that their actions were wrong but was nevertheless unable to prevent his own stealing.

Following lunch, the data blitz sessions took place in the enchanting backdrop of the Dorchester library, housing one of the most significant collections of rare books in the world. Tea, coffee and desserts were served whilst digital poster presentations (available now on the BNPA website www.bnpa.org) were streamed, each 3 minutes in length, followed by quick-fire Q&As with the authors. Posters were of an excellent standard and covered a wide range of topics, with the poster prize winners announced shortly after:

- Heather Smyth - 'In a mist?' – What is 'brain fog'?
- Isabel Mason - Functional neurological disorder in the chronic pain clinic; a retrospective study of comorbidity
- Saurabh Sonkusare - Frequency dependent emotion differentiation and directional coupling in amygdala, orbitofrontal and medial prefrontal cortex network with intracranial recordings

Dr Wendy Phillips, BNPA Director, finished the theme with Medicolegal Clinical Case Presentations, accompanied by fellow Consultant Neurologist Dr Mark Manford, who gave a talk on epilepsy (and associated TBI), with the thought provoking statistic that 20% of patients at tertiary clinics with the diagnosis of "uncontrollable epilepsy" do not have epilepsy. The audience were treated to an exciting panel discussion with Professors Jon Stone and Michael Kopelman, BNPA Secretary Dr Vaughan Bell, and barristers Jonathan Dingle and Andrea Barnes. We enjoyed both clinical and legal interpretations and perspectives of the cases, not always in agreement, but certainly backed with solid argument, whilst offering our own thoughts via the Slido App.

Then began the theme around our so-called hidden sense: interoception. The audience received a boost of post-prandial energy from the riveting and enthusiastic talk by Professor Sarah Garfinkel on "Dissociating dimensions of interoception in neuropsychiatry." Shining light on the interoceptive channel from the heart, Professor Garfinkle spoke about how afferent signals interact with neuronal mechanisms to alter emotion processing, but also how this is disrupted in neuropsychiatric conditions, impacting symptoms such as dissociation and anxiety. A highlight of the talk was the exciting data showing how interoceptive training for autistic people might alleviate anxiety through improved bodily awareness.

We then delved into "the self" and interoception with Professor Aikaterini Fotopoulou's invigorating talk on "Integrating dimensions of interoception in neuropsychiatry." Thought provoking to say the least, Professor Fotopoulou discussed interoceptive monitoring difficulties in anorexia nervosa. The relevance here is belief updating and how rigid behavioural control might be used to resolve the intolerable uncertainty of interoceptive states in anorexia nervosa. Interoceptive therapies using biofeedback offered future hope within this area.

Our keynote talk of the day was by renowned author and Professor of Cognitive Neuroscience Adrian Owen OBE, titled "Into the Gray Zone: Assessing Residual Cognitive Function after Serious Brain Injury". Professor Owen described how the use of fMRI, EEG and functional near-infrared spectroscopy (fNIRS) can be used to detect covert conscious awareness in patients who are behaviourally entirely non-responsive, allowing some of these individuals to communicate their wishes and thoughts. Professor Owens also highlighted circumstances in which imaging cannot be used to infer awareness, enlightening us both clinically and neurophilosophically on the neural representation of our own thoughts and intentions.

Thursday evening ended with a pizza and drinks party, accompanied by the superb vocal harmonies of four-piece band The Party Faithful in the gardens of the Royal College.

Day 2 began with the unforgettable, captivating and slideless JNNP lecture by Honorary Professor of Psychiatry at the University of Birmingham, Femi Oyebode, whose introduction was inspiring in itself. Professor Oyebode guided us through the descriptive psychopathology of phantom limb, Charles Bonnet, musical hallucinations and autoscopy (carefully differentiating the feeling of presence, negative autoscopy, out of body experience and heautoscopy proper) and along the way inferred underlying brain processes. Professor Oyebode emphasised the value of psychopathology in theorising about neural mechanisms: "To be constantly interested in psychopathology, asking the right questions which are not there in checklists, matters as it also reveals so much more about how the brain works."

Then began the theme of inflammation, with a historical but also contemporary talk by Dr Mark Honigsbaum on "What can we learn from the nervous sequelae of past pandemics". Dr Honigsbaum examined the Victorian approach to the nervous sequalae trailing the "Russian influenza" of the 1890s, such as exhaustion and psychosis, which, unlike long-COVID, were more often documented in men than women.

Next, Professor Michael Benros (Head of Research at Mental Health Centre Copenhagen) spoke about "The epidemiology of infections as a risk factor for psychiatric illness", opening with a chronology of psychoneuroimmunology, from 400BC to present day. Using Danish registry and biobank data he showed how infections and autoimmune diseases increase the risk of developing severe mental disorders in a dose-response relationship. He also boosted our knowledge of the immunogenetic contribution to this and the recognition of the role of anti-inflammatories for neuropsychiatric sequelae.

The morning was rounded off by three 15 -minute members' platform talks; Dr Samia Elkommos (Dept of Neuroscience, Kings College), Alicia Smith (PhD student at University of Cambridge) and Dr Hailun Cui (Dept of Psychiatry, University of Cambridge). Dr Elkommos brought together depersonalisation and altered interoceptive processing with the heartbeat-evoked potential (HEP) in her talk on "Attenuated heart-brain integration predicts functional non-epileptic seizures," raising the HEP as a potential biomarker for functional seizures. Alicia Smith enriched our knowledge of memory with her presentation on "Aberrant emotional memory encoding in a transdiagnostic sample of patients with intrusive memories," showing how individuals with intrusive memories experienced greater sensitivity to negative stimuli and going on to report on the role of attention in this.

Dr Cui's presentation on the neuropsychological changes underlying the symptomatic relief in capsulotomy for refractory OCD, reported (using task-based fMRI) the importance of targeting connectivity between the nucleus accumbens and pregenual anterior cingulate cortex.

Following the BNPA AGM was another superb lunchtime data blitz, with Friday's winners:

- Laura Marsh - Inhibition of personal memory retrieval in dissociative amnesia: a study of two cases
- Tanmay Anand - Object drawing from name in semantic dementia provides evidence for graded, transmodal semantic knowledge

Our afternoon theme of neuromodulation commenced with a joint session with the American Neuropsychiatric Association, in which Dr Shan Siddiqi (Neuropsychiatrist and Asst Professor at Harvard Medical School and Brigham & Women's Hospital), gave an outstanding plenary talk on circuit-based targeting of brain stimulation treatments (such as TMS and DBS). He illustrated how neuromodulation can target different circuits for different symptoms (e.g. dysphoric vs somatic symptoms), but also how TMS and DBS can target the same circuit to treat the same depressive symptom, and how lesions can be used to identify TMS and DBS targets. The importance of personalised brain mapping in neuromodulation was highlighted in the treatment of psychiatric disorders.

In BNPA President Professor Valerie Voon's talk, titled "Neuromodulation of intracranial physiological recordings and behaviour," we were presented with illuminative studies indicating the physiological networks underlying negative emotional processing, anticipation of reward and loss, and risk taking. Professor Voon also showed how stimulation at specific frequencies might influence behavioural measures, and instilled therapeutic optimism with ways of refining neuromodulation parameters when treating related disorders.

Professor Colleen Hanlon closed the show with her talk titled "Saving Adam from the Apple: using transcranial magnetic stimulation as a transdiagnostically relevant tool to decrease cue-reactivity". Professor Hanlon bridged the worlds of neuromodulation and temptation with a transdiagnostic neural biomarker for cue reactivity: a network involving the ventral medial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), and insula. We were shown how continuous theta burst stimulation to the left frontal pole decreases drug cue-reactivity among heavy alcohol users and cocaine users. This also decreased frontal connectivity in this network and has been shown to reduce cue reactivity in PTSD and obsessive behavioural disorders.

The conference ended with a well-deserved and sustained round of applause and show of gratitude for our Executive Administrator Jackie Ashmenall and Conference Secretary Gwen Cutmore.

The next BNPA AGM will be held at the Royal College of Physicians, 2nd and 3rd March 2023.

The poster presentations can be viewed at https://bnpa.org.uk/2022-poster-gallery/
and the majority of the videos of the talks from the BNPA 2022 annual conference will be uploaded to bnpa.org, along with the abstracts.

International Lewy Body Disease Conference 2022

Conference details: 15-17 June 2022, Newcastle, UK. ***Report by:*** Dr Angelika Zarkali, Clinical Research Fellow, University College London. ***Conflict of interest:*** None declared.

This June, after a year's delay due to COVID, the international Lewy Body Disease community came together again in the biannual International Lewy Body Disease Conference in Newcastle. Over 3 days we saw a wide range of amazing talks by world experts in the field as well as early career researchers, whilst a concurrent carers stream organised by the Lewy Body Society further enhanced the conference's programme. An added plus were the excellent social events organised on both days in a splendidly sunny Newcastle!

The conference started with a welcome by two legends of Lewy body disease and of Newcastle University, Prof Alan Thomas and Prof David Burn who set the tone for a fantastic meeting. The scientific programme was too extensive to summarise, covering the whole range of Lewy body diseases: from genetics, to fluid biomarkers, prodromal disease, clinical symptoms, neuroimaging, therapeutics, neuropathology and mechanisms of disease. The format of each symposium, with six 15 minute sessions including both talks by senior researchers and clinicians and early career researchers kept everyone alert and engaged.

A key theme from the conference was moving away from a research focus on only Dementia with Lewy bodies (DLB) to applying lessons from wider related disorders. This was a common theme throughout the conference: in a plenary on clinical synucleopathies, Prof Ron Postuma from McGill University discussed the link between REM sleep behaviour disorder and how it can be a useful area of study to better understand prodromal disease in both DLB and Parkinson's disease (PD). Further highlighting this point, Dr Sonja Scholz, NIH, during the genetics symposium highlighted the results of a recent gene wide association analysis (GWAS) of DLB which found that DLB genetic risk is a complex overlap of Alzheimer's disease and PD. Similarly, Dr Aaron Wagen, UCL, reported findings of shared heritability between DLB, PD and Alzheimer's when looking within specific loci of the genome, specifically SNCA and APOE4, although this only explained approximately 50% of the genetic risk of the disease. Finally, the importance of vascular pathology in DLB was highlighted from a dual perspective: in the neuropathology symposium, Dr Lauren Walker, Newcastle University, highlighted cerebral amyloid angiopathy (CAA) which occurs both in DLB and PD dementia but with a different topographical distribution and with type 1 CAA more common in DLB, whilst in the neuroimaging session, Prof Daniel Ferreira, Karolinska, talked about the differential contribution of cerebrovascular disease in grey matter degeneration in DLB.

Another key theme was the emergence of novel techniques and biomarkers which may be useful both in better understanding mechanisms of disease as well as for diagnosis and patient stratification in clinical trials. One new possible biomarker is EEG as highlighted by Dr Julia Schumacher, Rostock, with a shift to slower frequencies in DLB which is already seen in patients with mild cognitive disorder suggestive of Lewy body disease (MCI-LB) compared to both MCI with likely Alzheimer pathology and controls. Although more standardisation of EEG is needed, its wide availability, ease and low cost could make it a potentially useful marker to better diagnose MCI. Blood biomarkers are also emerging for disease monitoring and diagnosis as discussed in depth in a dedicated symposium chaired by Prof Omar El-Agnaf, Qatar Biomedical Research Institute and Prof Henrik Zetterberg, University of Gothenburg: progress in alpha-synuclein assays, plasma p-tau and amyloid markers marks an exciting time in the field.

Finally, the last important theme of the conference was the need for better phenotyping of the disease, which may allow for better classification and prognostication at the individual level. Dr Eli Matar, Sydney University talked about symptom clustering techniques and how they may inform better diagnosis, but also provided insights on pathophysiology and neuropathology, whilst Dr Anna Injuanzo, Karolinska talked about MRI-driven clustering of DLB subtypes that show different longitudinal cognitive performance and disease progression.

The conference also boasted a "Living with Lewy body" parallel stream where people living with Lewy body diseases and their families were able to hear about latest research but also network with other people living with dementia and their carers and become "empowered through information." A joint session between the Scientific and Living with Lewy body disease streams with a personal story by Susan Williams, highlighted the importance of having the voices of individuals with the disease heard.

On the final day of the conference the Rising Star awards were presented with the Gold preclinical award going to Dr Daniel Erskine, Newcastle and the Gold clinical award to Dr Callum Hamilton, Newcastle. The packed 3-day meeting was drawn to a close with a debate on whether it is now time for a trial of an amyloid lowering agent in DLB with Dr Jim Galvin advocating for and Dr John Duda against the motion. The answer to the question is inconclusive, depending on who you ask, but the debate highlighted the complexities of the issue and was an interesting and entertaining conclusion to the conference!

Having provided an opportunity for learning as well as meeting and networking with peers worldwide and individuals living with Lewy body disease this was an amazing meeting – with all delegates looking forward to meeting again in 2024!

Pharmacology Case Studies for Nurse Prescribers

Authors: Donna Scholefield, Alan Sebti and Alison Harris
Published by: M&K Publishing
Edition: 2nd (2021)
Price: £45
Pages: 474
ISBN: 9781910451250
eBook: 9781910451755
Reviewed by: Orlagh Jones, Advanced Nurse Practitioner. Ysbyty Gwynedd, Bangor.

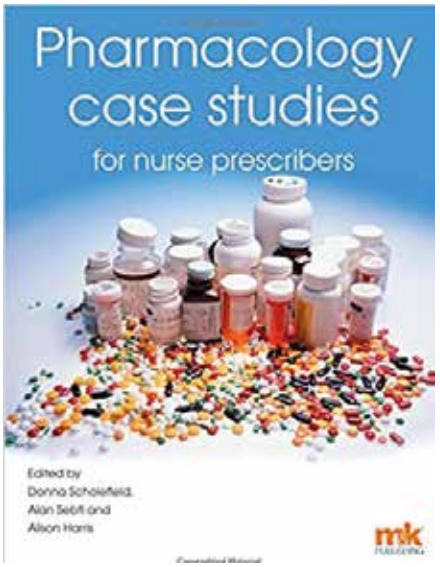
This second edition of the Pharmacology case studies for nurse prescribers has been carefully revised with the most recent research and guidance from NICE, the British National Formulary (BNF), the Royal Pharmaceutical Society (RPS), the Nursing and Midwifery Council (NMC) and the Royal College of Nursing (RCN). It consists of twenty-two chapters, sixteen of these, case studies for common specific patient conditions from angina to neurological disease. There are new chapters on pregnancy and breastfeeding, sexual health and contraception, frailty and effective use of the British nation Formulary (BNF). The latest developments in pharmacology are included in the text.

The book is aimed at students undertaking the non-medical prescribing (NMP) course, however it is a valuable resource to all registered nurses and qualified nurse prescribers. Furthermore, it would be a worthwhile tool for lecturers on the NMP programme and pharmacology modules alike.

Each chapter has case studies, activities and self-assessment questions that link the theory of pharmacology to practice, and a thorough glossary. The answers to all activities are included at the end of each chapter and it challenges and induces reflection by applying theory to real clinical cases. It is a useful tool for experienced prescribers to use to formally reflect and complete CPD hours. Clear links to further sources of learning are provided in each chapter.

The clearly written text is easy to understand, and supported by diagrams and tables where appropriate. The final chapter 'insights into professional prescribing' ties in the reflection aspect and the accountability imposed by the RPS framework. The only limitation is highlighted itself within chapter four, when discussing the BNF paperback as the time between creation and publication can render some content out of date. The same applies to some of the information in the book, however, provided the reader remains mindful of this, this is an interesting supplement to the NMP course.

By employing the case study approach, it supports the reader to combine pharmacological



theories with clinical practice. Reading this book, and carrying out the numerous self-assessment activities, will give the reader an appreciation of the value of having a sound pharmacological knowledge in order to deliver safe, effective prescribing practice and ultimately improve the quality of patient care.

Neurotrauma and Critical Care of the Brain

Edited by: Jack Jallo and Christopher M. Loftus
Published by: Thieme
Edition: 2nd (2018)
Price: £177.20
No. of Pages: 416
ISBN Number: 978-1-62623-336-2
Reviewed by: Nicole Lichtblau, King's College Hospital, London.

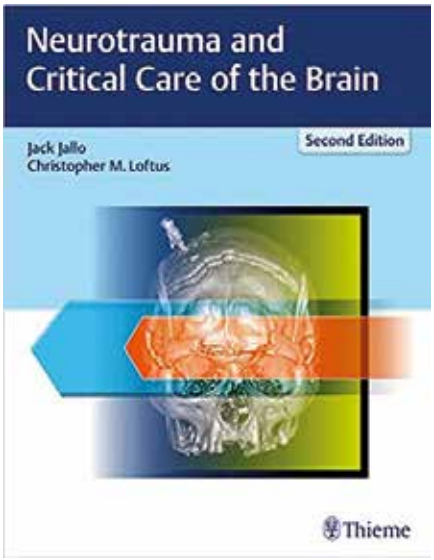
This comprehensive and brilliantly illustrated textbook covers all aspects of traumatic brain injury and its acute care. Edited by the two US neurosurgeons Jack Jallo and Christopher M Loftus, it is not just a perfect resource for neurosurgical colleagues but in fact for all specialties involved in the care of patients with traumatic brain injury (TBI), including the emergency care doctor, intensivist and the neurologist.

Starting with a historical background and epidemiological facts of traumatic brain injuries they are setting the scene for the relevance and frequency of TBI and how treatment standards have evolved. The next chapters are covering the basic concepts of TBI classification, pathophysiology and neuroanatomy with various tables and illustrations serving as a quick reference and to visualise complex contents.

The final chapters then focus on monitoring and treatment at different stages – pre-hospital, Emergency Department, Intensive Care through to Neurorehabilitation. The authors summarise nicely the English literature up to 2016 and set out what current standards should be. In that they also emphasise the differences in certain groups of TBI, such as military or paediatric cases. Even though often referring to the US healthcare system, it is still literature worthwhile reading outside the US. The book also offers insights into creating guidelines and treatment standards. Some chapters focus on research needs and this book therefore is of relevance to academic and managerial tasks of clinicians.

It only has a few shortcomings. From a neurologist's perspective, I would have wished for more extensive review and discussion of treatments for neurological complications of TBI, such as post-traumatic headache, vertigo, epilepsy, cognitive and behavioural symptoms. Even though they are all mentioned to some degree throughout the different chapters, their treatment approach is less well discussed as other aspects of treatment, such as VTE prophylaxis, nutrition and respiratory needs.

The whole book is generally well written and nicely illustrated. However, it might have benefited from more careful editing to make it a coherent textbook. As it is, it is rather a



collection of review papers written by different authors. This leads to a lot of repetition and at times slightly different opinions on the same topic. But overall a comprehensive review on traumatic brain injury and its management, this book will be a valuable source to those treating patients with TBI.

Therapy Outcome Measures (TOMS) Connect 2022

Conference details: 15 November 2022, Online.

The Development and Trial of a Patient Centred Multi-Disciplinary Team Stroke Outcome Measure in South West London

Organisation
Croydon Health Services NHS Trust

What outcome measures did you use? e.g. TOMs
MDT Stroke TOMs - in progress

Summary of work
Outcome measures in stroke have previously lacked holistic Multi-Disciplinary Team (MDT) involvement and are often time consuming to administer. The MDT Stroke 'Therapy Outcome Measure Scale' (TOMs) was developed as a quick psychometrically robust, clinical outcome measure within Croydon's Stroke Team to encourage MDT collaboration, patient centred care and communication between all team members and with the patient. It was also developed to monitor trends within the service and highlight areas in need of change, resources or development.

The MDT Stroke TOMs was developed iteratively with the multidisciplinary team by adapting the previous Stroke TOMs to include cognition, communication and swallowing. Over 112 members of the MDT staff across South West London were trained virtually in theory and inter rater scoring practice sessions. Feedback on the scale and trainings was gathered electronically via a virtual questionnaire. The MDT Stroke TOMs has been in trial across the community stroke teams in South West London for nearly 1 year.

Key benefits
Now being used across 6 community integrated, interdisciplinary stroke teams. - 90-97% of trainees found the TOMs training useful, engaging, relevant with 91% feeling the MDT Stroke TOMs was a positive development. - MDT approach to patient discussions, goal plannings and outcome measurement - Holistic scoring of stroke patients - Now being used in SW London for all neuro patients.

Key outputs
MDT Stroke TOMs: hopefully printed by the end of the year for use.

Key learning points
Scoring and discussion around patients in stroke, can benefit from being MDT led. - The Stroke MDT TOMs is quick and easy to use with high interrater reliability. - Positive feedback from the enitre MDT team about its uses - Importance of patient centred MDT care in stroke.

Funding / resources deployed
Croydon Health Services

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The Evolution of TOM training delivery: Face to face in person to face to face using MS Teams

Organisation
South Warwickshire University NHS Foundation Trust

What outcome measures did you use? e.g. TOMs
Therapy Outcome Measure (TOM)

Summary of work
The TOM trainers within the community and hospital-based AHP groups met to determine a way forward to deliver TOM training to the various professional groups during the Corona virus (COVID 19) pandemic. Having reached agreement from AHP leads that TOM would be the overarching outcome measure used prior to the pandemic, there were still many therapy staff that required training in how to administer the TOM. As MS Teams was the meeting platform of choice within the Trust, it was decided to use this platform to deliver the training. These were set up as multidisciplinary training sessions (not uni-professional), with a maximum of 10 attendees and 2 trainers facilitating the sessions. A slide presentation was used to deliver the theory. Break out rooms were used to split attendees into 2 equal groups to allow for practice of TOM scoring and discussion of scores attributed. Formal feedback regarding the running and delivery of the sessions was obtained, with adjustments made in relation to the feedback received where necessary.

Key benefits
1. Evolution of the MS Teams training offered based on feedback from attendees and also through MS Teams training sessions.
2. More therapy staff trained in the use of TOM.
3. Awareness of need to input scores into EPR used by professional group.
4. Professional groups where staff are unaware that TOM is the outcome measure of choice have taken action within their groups to identify 'champions' to take the agenda forward. This includes training trainers and ensuring their EPRs are optimised for recording the TOM.

Key outputs
1. Identified the need to establish a more sustainable way to train staff in the future. An option where staff attend training at their and the team's/service's convenience would be preferable, potentially coupled with opportunity to meet with TOM trainers if desired or necessary.
2. Professional groups to ensure that their EPRs are optimised for appropriate TOM score recording by speciality and team.

Key learning points
1. Although it was hoped that using MS Teams would be more sustainable in terms of improving staff's ability to attend the sessions, factors such as patient flow pressures, therapy staff's perception of the relative importance of attending the sessions, and sickness absence still impacted significantly on attendance levels.
2. The TOM trainers are a limited and fluctuating resource, so a more sustainable method of training delivery is required that staff can access at the appropriate opportunity for them.
3. It should never be assumed that all professional groups are aware of the TOM as the outcome measure of choice. Some professional groups had embedded the use of the TOM into their practice already, where others had never heard of it. This influenced their motivation to sign up for the training, and then with engagement in it.
4. Therapy staff were not aware of how to capture TOM scores digitally in their electronic patient records (EPRs), and equally, some of the professional groups had not had this feature developed optimally in their EPRs (scales, teams, aetiologies) as they had not yet started using the TOM.
5. More than one EPR is used within the Trust (Lorenzo, EMIS, BEST), so training needs to take this into account.

Funding / resources deployed
1. TOM 'Train the Trainer' training for identified representatives in each of the participating AHP groups.
2. Releasing capacity from service delivery for trainers to deliver TOM training.
3. Releasing capacity from service delivery for trainers to attend monthly meetings to review training sessions offered to feedback on successes and barriers to success, and implement changes.
4. MS Team training for trainers to advance their training delivery using tools available in Teams.

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The Tale of TOMs and Talking Mats™

Organisation
Communication Aid Service East of England (CASEE) based at Cambridge University Hospitals NHS Foundation Trust

What outcome measures did you use? e.g. TOMs
TOMs and Talking Mats (TM) with specific CASEE PROM questions

Summary of work
Comparison of our Patient Reported Outcome Measure (PROM) with our clinician reported outcome measure TOM-AAC for a selection of patients seen by CASEE.

CASEE created a PROM using the Talking Mats™ technique with 2 questions designed to compliment the TOM-AAC.

Activity Domain Question
1. This is about the different things the patient wants to communicate about.
'How do you feel you are able to tell people your needs; share a story; give your opinion?'

Participation Domain Question
2. This is about who the patient is communicating with. 'How do you feel about your communication with friends'; with carers; with your SLT etc.?'

Over the years of using both outcome measures we hypothesise there is a complimentary relationship between the Talking Mats™ (PROM) and the TOM-AAC activity and participation domains.

This poster shows the work completed to compare TOMs change scores with Talking Mats qualitative changes to see if patients and clinicians have a similar or different perspective for the outcome achieved.

Enabling the team to evaluate the use of these two tools in combination and identify further questions to explore to ensure we are measuring outcomes accurately from both a clinical and patient view.

Key benefits
· Capturing service outcomes alongside patient voice
· Opportunity for clinicians to reflect on outcomes from differing perspectives
· Using a talking mat to gather qualitative information may help clinicians to understand outcomes in more depth and better represent the true impact of intervention

Key outputs
· Standardised Talking Mat PROM questions and resources for team to use
· Inclusion in CASEE training for local professionals

Key learning points
· Clearer understanding of TOM-AAC domains by the team · Better understanding of patient experience and more valid and reliable TOM-AAC scoring · Opportunities for service evaluation in light of this data

Funding / resources deployed
N/A

Contact for further information
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Implementation of the Therapy Outcome Measure: Our Journey so far

Organisation
South Warwickshire University NHS Foundation Trust

What outcome measures did you use? e.g. TOMs
Therapy Outcome Measure

Summary of work
After excluding other outcome measures, we decided to adopt the Therapy Outcome Measure (TOM) as a more widely applicable, easily and quickly administered outcome measure in 2009.

We began our journey with TOM as an Occupational Therapy service within a community trust, before merging with the local acute trust in 2010, expanding the specialities covered by OT.

Initially TOM scores were captured on paper with no way of collating the data other than through manual inputting to spreadsheets. The acquisition of a suitable external electronic reporting system was cost-prohibitive to the OT annual budget, and the scale of the project too small to secure resource and funding for the development of a sustainable in-house data collection and reporting system.

In 2016, in line with national drivers to report patient outcomes, other Allied Health Professionals (AHP) groups (Podiatry & Orthotics, Dietetics, SALT, Physio) joined the OT service in the use the TOM as their profession-specific outcome measure. With the addition of the other AHP groups, a critical mass was achieved that made it possible to secure resource for the development of the TOM data collection form within electronic patient records (completed in 2018) and have a central dashboard developed for reporting purposes (2020).

Key benefits
· A single outcome measure, simple and quick to use, that can be used by the wider MDT and that therapy staff are conversant in. · The 'critical mass' created by the AHP body through being able to access and use an outcome measure applicable to most disciplines, generated enough gravitas for the Trust to back assimilation of the recording of TOM into EPRs and to create a dashboard for reporting purposes. · Collaborative working between TOM trainers to train AHP therapy staff in the use of TOM. · Collaborative working between TOM trainers towards the development of a more sustainable, progressive training offer for the future, countrywide.

Key outputs
· An overarching outcome measure has been included into daily clinical practice for the benefit of the patient, which can be used to review the effectiveness of the services provided. · Inclusion of TOM data inputting into Lorenzo and EMIS, the locally used electronic patient records. · Creation of a TOM reporting dashboard accessible to all AHP services from different electronic patient record sources. · Access to a sustainable training package in the use of TOM in clinical practice. · Develop and maintain TOM trainers accessible across AHP groups.

Key learning points
· Start somewhere. We started with piloting TOM in our stroke service, then rolled it out to the wider OT service. engagement of clinicians is essential from the start. · Don't go it alone. Always look to see whether there is a wider need for the same resource. · It required a significant need from a significant number of staff groups. Backed by professional standards of practice, we generated the economy of scale to gain 'buy-in' and secure resource, in this case to invest in effective digital means of data capture, assimilation of data, and reporting mechanisms. · The 'chicken and egg' of having sufficient staff trained to be contributing into digital data capture. It is difficult to check that data pulling into the dashboard for reporting purposes is accurate if there is a dearth of inputting created by a low number of AHP staff trained in the use of TOM. · Never assume that all staff groups have generated equal amounts of 'buy-in' from their staff members. This can create substantial barriers to trainers through lack of engagement from therapy staff attending the training. · Replenishing TOM Trainers will be a constant challenge as they leave to assume new roles elsewhere. · A sustainable means of staff access to TOM training is an essential as we still have a substantial training backlog (2022).

Funding / resources deployed
Human resource · Local AHP TOM trainers. Engaging clinicians to be trainers relies on them committing their time to the preparation and running of the sessions, while also carrying caseloads, managing pressure on in-patient flow and ongoing staff cover issues related to absence. Training sessions were offered to all AHP groups via MS Teams through the course of 2020/2021, linking with Dr Neil Bindemann and Prof Pam Enderby's work on developing a sustainable TOM training programme for the future. · Information team. The dashboard, developed in Tableau, is still undergoing refinement. The quality and quantity of information being received is being tested and is very much dependent on the number of AHPs trained, using and inputting TOM scores for the patients they see. · Lorenzo & EMIS ICT team. The development of the TOM data collection form within electronic patient records was completed in 2018. · AHP Managers. Working in collaboration and co-operatively to agree on a single outcome measure, support their trainers to train and their staff to attend training session. Admin support. Initially the admin team supported with the collection of paper TOM recording sheets and inputting of the data to spreadsheets. Later they supported with rallying staff to establish demand for TOM training and to get them organising their diaries so that they could attend. Financial resource · The OT manager presented for approval the need for a dashboard for reporting purposes at the Trust's digital board in October 2019 in a bid to secure human and the financial resource that this incurs through use of their time. · Training for the AHP TOM Trainers to be able to cascade their knowledge in the use of the outcome measure. The initial TOM training sessions, followed by 'Train the Trainer' learning sessions were commissioned in 2020, to develop local TOM trainers from each of the AHP groups.

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Phone, Video and In Person – Value based Speech and Language Therapy Rehabilitation with Deaf Children and Young People

Organisation
ABUHB Speech and Language Therapy

What outcome measures did you use? e.g. TOMs
TOMs Service user feedback Patient story - but won't be able to include in the poster. Not an outcome but part of the study I used performance data to provide information on value.

Summary of work
Due to the impact of COVID 19 the way in which the ABUHB SLT deafness team delivered their service changed and resulted in deaf children and young people (DCYP) receiving a blended approach to intervention. A blended approach means that DCYP received a combination of telephone, video, and face to face appointments with the Speech and Language Therapist and/or Speech and Language Therapy Assistant delivered in their home and/or educational setting.

A blended approach has proven to be an effective and efficient model of intervention for DCYP in Gwent. This approach has:
1. Maintained and improved patient outcomes for this population of children whilst delivering person centred care. Service user feedback from parents/carers and school staff indicates that 90% of them value a blended approach to intervention.
2. Doubled the amount of contacts that the speech and language therapy deafness team are able to provide therefore increasing productivity.
3. Reduced travel expenses by 49.85%

Key benefits
Although there is no prescriptive intervention plan for a blended approach to service provision, it is clear from this study that a blended mode of delivery provides value-based care as it doubled productivity and reduced costs without compromising on outcomes for DCYP. Most responses from service users also supported this approach even though they still favour in person appointments. This is understandable as COVID 19 has forced families to make personal and professional changes and change can be overwhelming. In a study evaluating barriers to adopting tele-medicine as an approach to intervention, Kruse et al (2018) reported technological maturity, resistance to change due to the fear of the unknown, time to understand the value/reasons of the change and level of education of the patient and/or care giver as the most common barriers. Training, sharing/discussing the positive outcomes of the DCYP along with time to adjust may go some way in addressing this.

Key outputs
A blended approach to intervention is an effective and efficient service model for this client group as it is outcome focused and provides value-based care. Blended care provides the opportunity to integrate treatment modalities to establish individually tailored care plans for DCYP depending on their needs. The ABUHB deafness service will continue to offer this model of intervention ensuring that service users receive the support they require to understand the rationale behind the approach along with the positive outcomes that are being achieved. This study will be shared within professional networks to support service provision and decision making in other localities.

Key learning points
1. Keeping service users at the heart of the model. Engagement with and giving them a voice is paramount to the success of service transformation particularly in hard to reach populations such as deafness.
2. Challenge professional attitudes that highly specialist clinical interventions can be provided through other modalities.
3. A blended offer is suitable for the deaf population providing a blanket approach is not used.
4. Important to share the outcome of this study to support the learning of others.

Funding / resources deployed
Completed within role therefore no additional funding used.

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The blood brain barrier and Lina Solomonovna Stern (Shtern)

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Abstract
The blood–brain barrier (BBB) regulates the transport of molecules between the central nervous system (CNS) and blood. It consists of two components: the vascular endothelial cells forming so–called tight junctions, and the blood–cerebrospinal fluid barrier. It plays an important role in the pathogenesis and in recovery from many cerebrospinal disorders.

Paul Ehrlich was the first to observe in mice that intravenously injected acidic dyes stained the tissues of the body but not the brain. He deduced there was a barrier between systemic blood and nervous tissues. His pupil Lewandowsky visualised a capillary wall that blocked the entrance of certain molecules. And, Edwin Goldman injected trypan blue into the CSF and observed that the brain but no peripheral organs was stained — indicating the dye could not cross from CSF to the systemic bloodstream, but could leave the blood vessels of the choroid plexuses within the ventricles to enter the brain tissues.

Experiments of the heroic Russian Lina Solomonova Stern (Shtern), persecuted by Stalin, formulated the rule that every substance contained in the blood must penetrate the cerebrospinal fluid before it can exercise its effects on the nerve elements; she named the blood–brain barrier: barrière hémato–encéphalique. This short essay was prompted by the poignant biographical article about Lina Stern [1], whose work on the blood–brain barrier (BBB) was unknown to me.

The blood–brain barrier (BBB) regulates the transport of molecules between the central nervous system (CNS) and blood. It regulates the composition, homeostatic and immune environments of the nervous system and the exchange of informational molecules. As a barrier it prevents toxic blood components, and pathogens from entering the brain. In disease, its breakdown can cause leakage of toxic blood elements into the CNS.

Clinically, BBB dysfunction [2] plays an important role in the recovery from acute forms of brain injury, strokes and seizures and in neurodegenerative disorders [3] such as multiple sclerosis and motor neuron disease.

Early experiments

Paul Ehrlich [4], whose studies on immune defense mechanisms culminated in the Nobel Prize, when looking for therapeutic agents, observed in mice that intravenously injected acidic dyes stained the tissues of the body but not the brain. He deduced there was a barrier between systemic blood and nervous tissues. However, he did not accept that permeability of cerebral vessels was different from that in other organs. Ehrlich's pupil the neurologist Max Lewandowsky identified sodium ferrocyanide in the urine of animals within 30 minutes after intraspinal CSF injection. And he observed effects of ferrocyanide on the CNS following intrathecal injection but not after intravenous administration. He did not use the term Blut–Hirnschranke (as commonly mis–reported), but he plainly visualised a barrier when he stated: the "capillary wall must block the entrance of certain molecules [5]."

Neurodiem

Another of Ehrlich's students, Edwin Goldman's experiments with the dye trypan blue confirmed this. When he injected trypan blue into the CSF the brain but no peripheral organs became heavily stained. This showed that the dye could not cross from CSF to the bloodstream, but could leave the blood vessels of the choroid plexuses within the ventricles: "Die Weg über den Liquor" [the way through the CSF] [6]. This barrier served to isolate the brain from other tissues; the extracellular fluid of the CNS is isolated from the blood.

McIntosh and Fildes in 1916 localised the BBB to the brain capillaries and recognised that CSF was not an intermediate compartment between blood and brain [7].

The blood brain barrier

The BBB consists of two components: 1. the vascular BBB, consisting of the endothelial vascular bed, and 2. the blood–cerebrospinal fluid barrier, consisting of the choroid plexus, which is a second boundary between the bloodstream and the central nervous system. It is formed by tight junction cells of the choroid plexus [8]. The anatomical site of the BBB is in brain endothelial cells (ECs) of blood vessels, which are wedged extremely closely to each other, forming so–called tight junctions. These allow only small molecules, fat–soluble molecules, and some gases to pass freely through the capillary wall and into brain tissue. Ninety–eight per cent of small molecule drugs do not cross the BBB. Some larger molecules, such as glucose, can gain entry through transporter proteins. The BBB and the blood–CSF barrier of the choroid plexus are functionally and anatomically distinct. Surrounding these vascular endothelial cells are other components of the blood–brain barrier, which communicate with the cells that form the barrier to modify its workings. This physical barrier consists of communicating junction between microvascular ECs modified by pericytes, neurons and astrocyte footplates. There is also a metabolic barrier regulating the free diffusion of soluble compounds by the expression of specific enzymes.

Barrier cells contain receptors and transporters and they can secrete substances such as cytokines, nitric oxide, and prostaglandins from either their CNS or peripheral side. Most drugs affecting the brain cross the BBB by free diffusion owing to high lipid solubility and low molecular weight [9].

Lina Solomonova Stern (Shtern) (1878–1968)

A major contributor to our understanding of the BBB is the now forgotten Lina Stern. In the 1920s, Stern published her early studies that clarified the concept of the blood–brain barrier (BBB) first indicated by Paul Ehrlich. Her experiments elaborated the physiology of this complex cerebral mechanism protecting cerebral function, later verified by Karnofsky in the 1970s using the electron microscope.

With Raymond Gautier, Stern confirmed this barrier or interface in numerous experiments and publications [10,11]. Inspired by Constantin von Monakow she formulated the rule that every substance contained in the blood must first penetrate into the cerebrospinal fluid before it can exercise its effects on the nerve elements, shown either by its physiological effects or by chemical analysis.

The blood–brain barrier (BBB) was a name she coined as barrière hémato–encéphalique [1].

> *We found that substances introduced into the general circulation could not all be detected in the CR. [cerebrospinal fluid] and that, on the other hand, all the substances introduced into the CR liquid were found at the end of a more or less long time in the general circulation. We have concluded that there is a kind of partitioning preventing the entry of certain substances into the CR, but allowing the release into the blood of any substance introduced into CR. At this partitioning, we have given the name of a hematoencephalic barrier.*
> Stern & Gautier 1922

Stern was born in 1878 in Tsarist Russia's Latvia. Her grandfather was a rabbi. Refused medical training at Moscow University, she entered Geneva University's medical school, graduating MD in 1903.

She embarked on original research and published extensively. Her researches included electro-stimulation of the heart, cellular metabolism, oxidation, cellular respiration, and central nervous physiology. With Frederic Battelli, Stern published 54 articles on cellular metabolism. In 1918 a new department of "Physiological Chemistry" was established at the University of Geneva where she was appointed the first woman Professor. There her work on the blood–brain barrier flourished. She published articles, on the penetration of many drugs into the brain, cerebrospinal fluid, brain homeostasis, and the blood–brain barrier in the developing brain.

But, aged forty–eight, against the counsel of her colleagues, she left this comfortable Swiss life in 1925 to become the head of physiology at the Second Moscow State University. She was widely revered and in 1929 became the director of a new institute of physiology and was elected to full membership of the Russian Academy of Sciences.

She became an advocate of suboccipital instillation of streptomycin for tuberculous meningitis, which proved effective. Two years after Hitler invaded Russia in 1941, she was awarded the Stalin Prize for her outstanding achievement in the research of the blood–brain barrier. However, as the Russians were pushing the German army back out of Russia, the paranoid Stalin decreed that Soviet Jews were infected with Zionism and part of an American threat to Russia. Her institute was disbanded and she was sacked [1]. In 1949 she was aged 71; on Stalin's directions she was imprisoned for three years and subjected to repeated physical beating [12]. Other Jewish anti–fascists were tried in 1952 and all except Stern were executed.

After Stalin died in 1953 the military court reversed his judgments. The 76 year old Stern returned undaunted from exile and again headed the physiology laboratory at the USSR Academy of Science until her death. She remained academically active and organised international meetings.

After her ordeals, she died on March 7, 1968, an accomplished pioneering scientist and a woman of extraordinary courage. She was buried at Novodevichij cemetery in Moscow.

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