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ACNR

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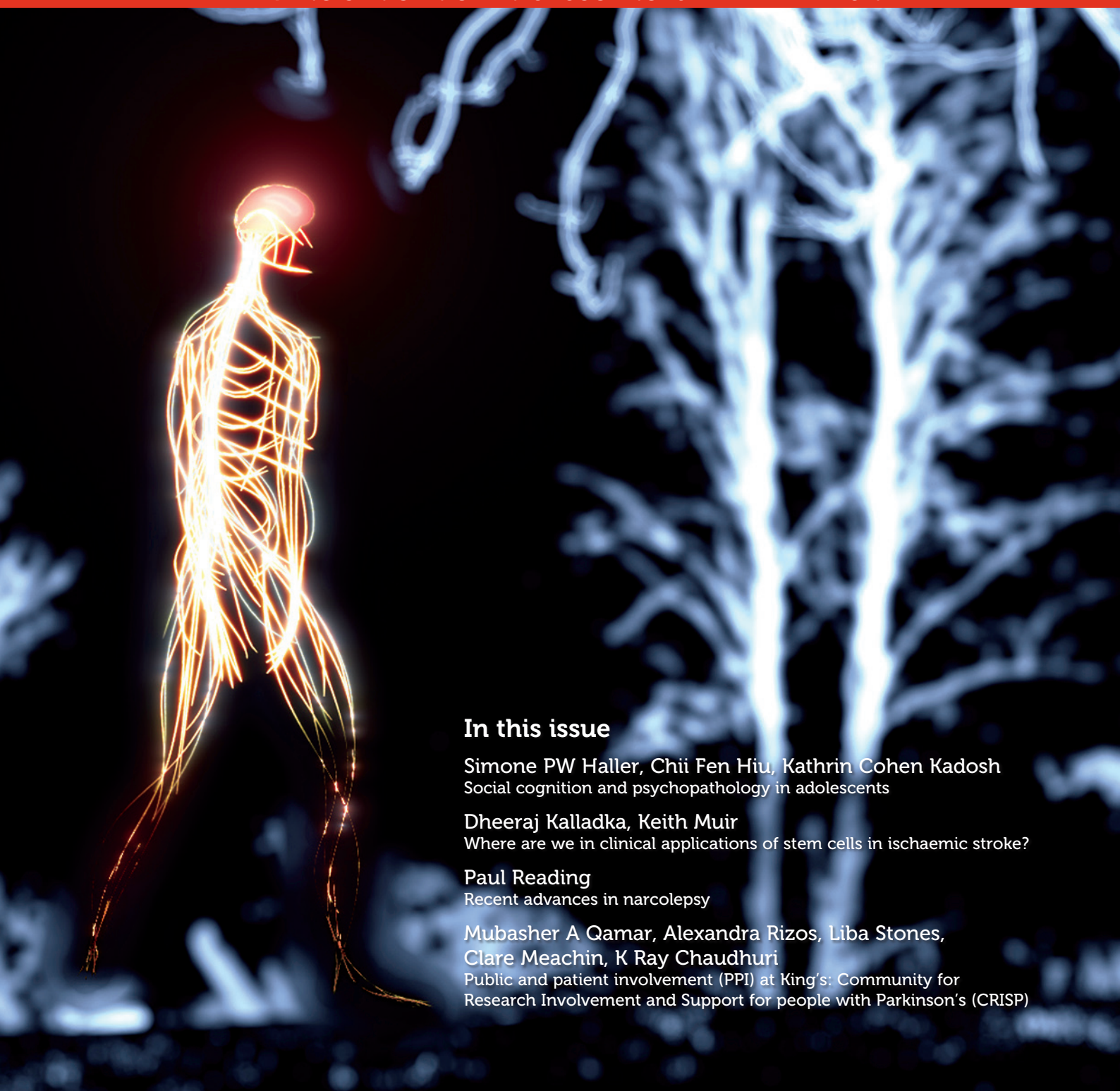
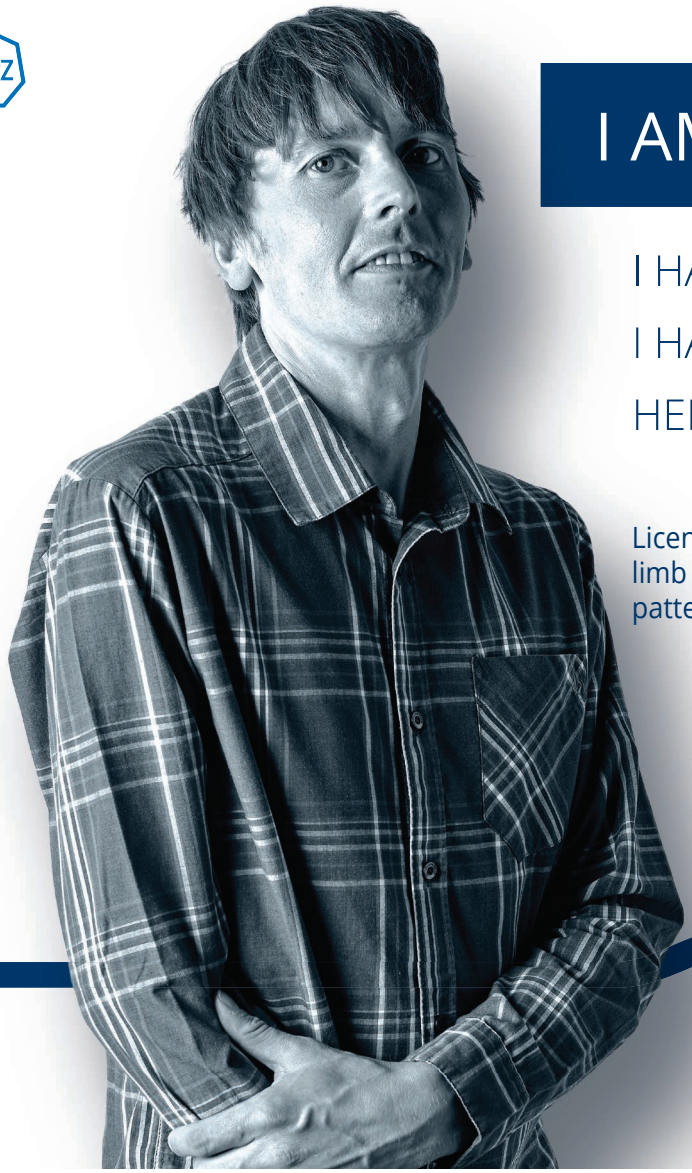
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue



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Should not be used during pregnancy unless clearly necessary. Should not be used during breast-feeding. ***Blepharospasm:*** Careful testing of corneal sensation should be performed in patients with previous eye operations. Due to its anticholinergic effects, it should be used with caution in patients at risk of developing narrow angle glaucoma. ***Spasmodic Torticollis:*** Patients should be informed that injections of Xeomin for the management of spasmodic torticollis may cause mild to severe dysphagia with the risk of aspiration and dyspnoea. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may decrease the occurrence of dysphagia. 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Frequency by indication defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); *very rare* (< 1/10,000); *not known* (cannot be estimated from the available data). ***Blepharospasm:*** *Very Common:* Eyelid Ptosis, dry eyes. *Common:* Headache, facial paresis, blurred vision, visual impairment, diplopia, increased lacrimation, dry mouth, dysphagia, rash, injection site pain, fatigue, muscular weakness. ***Spasmodic torticollis:*** *Very common:* Dysphagia. *Common:* Headache, presyncope, dizziness, dry mouth, nausea, hyperhidrosis, neck pain, muscular weakness, myalgia, muscle spasm, musculoskeletal stiffness, injection site pain, asthenia, upper respiratory tract infection. ***Post-stroke spasticity:*** *Common:* Headache, dysaesthesia, hypoaesthesia, dysphagia, muscular weakness, pain in extremity, feeling hot, and injection site pain. Flu-Like symptoms and hypersensitivity reactions also have been reported. *For a full list of adverse reactions, please consult the SmPC.* **Overdose:** May result in pronounced neuromuscular paralysis distant from the injection site. *Xeomin® may only be used by physicians with suitable qualifications and proven experience in the application of Botulinum toxin.* **Legal Category:** POM. **List Price:** 50U/vial £72.00/€110.00, 100U/vial £129.90/€195.00, 200U/Vial £259.80/€390.0 **Product Licence Number:** PL 29978/0003, PL 29978/0001, PL 29978/0004; PA1907/001/001, PA1907/001/002, PA 1907/001/003 **Marketing Authorisation Holder:** Merz Pharmaceuticals GmbH, Eckenheimer Landstraße 100,60318 Frankfurt/Main, Germany **Date of Preparation:** August 2016 **Further Information Available from:** Merz Pharma UK Ltd., 260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire WD6 3SR. Tel: **+44 (0) 333 200 4141**

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Date of preparation: October 2016 M-XEO-UK1-0063

CONTENTS

NOVEMBER-JANUARY 2017

REVIEW ARTICLES

SPECIAL FEATURES

ASSOCIATION OF BRITISH NEUROLOGIST TRAINEES

REGULARS

PUBLISHED ON-LINE

Front cover picture: Picture courtesy of CMT UK. The image is a still from a CMT awareness film made by Douglas Sager, who has Charcot-Marie-Tooth. See news item on page 31.

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Todd Hardy, Co-Editor.

Welcome to the latest issue of ACNR. In this issue Dheeraj Kalladka and Keith Muir from Glasgow write about the current state of play with regard to mesenchymal stem cell therapy for ischaemic stroke. They summarise data from the existing small trials and discuss controversies in timing, administration and the source of stem cells, and potential mechanisms of therapeutic effect.

Paul Reading from Middlesborough writes a timely update on narcolepsy covering diagnosis, and discussing pathogenesis, including controversy about whether narcolepsy may be immune-mediated. Current treatments such as modafanil, the newer sedative, sodium oxybate and also the potential future role of hypocretin replacement are reviewed.

Mubashar Kumar, Alexandra Rizos, Liba Stones, Clare Meachin and Ray Chaudhuri from London provide an overview of the Community for Research Involvement and Support for people with Parkinson's (CRISP) being conducted at King's college. This is a patient and public involvement (PPI) initiative which aims to increase Parkinson's research and awareness. The principles underlying this approach are relevant across a number of areas of neurology.

Simone Haller, Chii Fen Hiu, and Kathrin Cohen Kadosh from Oxford write about how tracing the psychological and emotional changes that occur in adolescence may help to identify those adolescents with, or at risk of, psychopathology to allow appropriate intervention.

ABN trainee, Lou Wiblin from Newcastle, argues that neuropalliative care brings with it different needs and requirements from that of traditional cancer-focused palliative care.

In our Rehabilitation article, Claire Williams, Nick Alderman and Rodger Wood comment on innovations in the St Andrews-Swansea Neurobehavioural Outcome Scale (SASNOS), an instrument that arose from collaboration between these two rehabilitation centres and is now widely used in the assessment of neurobehavioural disability.

The Independent Neurorehabilitation Providers Alliance (INPA) from the UK write about challenges facing neurorehabilitation within the NHS.

There are also reviews of AAIC 2016 in Toronto, the Neuroinfectious diseases 2016 course in Ottawa, and the Obstetric Neurology 2016 meeting in London. Book reviews are from Lakshmi Kottidi Navakoti, AJ Larner and Christian Komandzik. We hope you enjoy.

Todd Hardy, Co-Editor
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Thanks to all our Peer Reviewers this year

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Profile

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3 XADAGO reduces concomitant pain treatments and pain-related scores on the PDQ-39 when used as add-on to levodopa[4]

Prescribing information

Xadago ▼ 50 and 100 mg film-coated tablets

Consult Summary of Product Characteristics before prescribing.

Legal Category: POM

Marketing Authorisation number and basic NHS cost: EU/1/14/984/001-005, EU/1/14/984/006. NHS list price: £69.00 x 30 tablets for both 50/100mg.

Presentation: Each film-coated tablet contains safinamide methansulfonate equivalent to 50 or 100mg safinamide.

Uses: Xadago is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.

Dosage and administration: Treatment with Xadago should be started at 50 mg per day. This daily dose may be increased to 100 mg/day on the basis of individual clinical need. If a dose is missed the next dose should be taken at the usual time the next day.

Method of administration
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Special populations:
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Elderly: No change in dose is required for elderly patients. Experience of use of safinamide in patients over 75 years of age is limited.

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Pregnancy: Women of childbearing potential should be advised not to become pregnant during safinamide therapy. Xadago should not be given during pregnancy.

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Warnings and Precautions:
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At least 7 days must elapse between discontinuation of Xadago and initiation of treatment with MAO inhibitors or pethidine.

Impulse control disorders can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Patients and carers should be made aware of the behavioural symptoms of ICDs that were observed in patients treated with MAO-inhibitors, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.

Safinamide used as an adjunct to levodopa may potentiate the side effects of levodopa, and pre-existing dyskinesia may be exacerbated, requiring a decrease of levodopa.

Xadago has no or negligible influence on the ability to drive and use machines.

Contraindications:
Hypersensitivity to the active substance or to any of the excipients. Concomitant treatment with other monoamine oxidase (MAO) inhibitors or with pethidine. Use in patients with severe hepatic impairment. Xadago should not be administered to patients with ophthalmological history that would put them at increased risk for potential retinal effects e.g. in patients with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.

Interactions:
Concomitant administration of dextromethorphan or sympathomimetics such as ephedrine or pseudoephedrine, requires caution.

Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors. In view of the selective and reversible MAO-B inhibitory activity of safinamide, antidepressants may be administered but used at the lowest doses necessary.

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Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors, such as hypertensive crisis, neuroleptic malignant syndrome, serotonin syndrome, and hypotension. Impulse control disorders; can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. Other serious adverse reactions include bronchopneumonia, basal cell carcinoma, leukopenia, delirium, suicidal ideation, glaucoma, diabetic retinopathy, eye haemorrhage, keratitis, papilloedema, hallucination, depression, compulsions, delirium, suicidal ideation, impulse disorders, myocardial infarction, hyperkalaemia, peptic ulcer, upper gastrointestinal haemorrhage, hyperbilirubinaemia, ankylosing spondylitis, electrocardiogram QT prolonged and fat embolism, photosensitivity.

Common undesirable effects include insomnia, dyskinesia, somnolence, dizziness, headache, Parkinson's Disease, cataract, orthostatic hypotension, nausea and falls.

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November 2016 UK_XAD_142

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Social Cognition and Psychopathology in Adolescence

Simone PW Haller *
is a MRC/Scatcherd-funded Ph.D. Student at the University of Oxford. She completed her undergraduate studies at the University of St Andrews and an MSc at the University College London. Her main research interest is the development of social cognition and emotion regulation across childhood and adolescence. She is particularly interested in how changes in social cognition and emotional responding in adolescence may make this developmental period a time of increased risk for the onset of persistent and distressing forms of social anxiety.

Chii Fen Hiu *
completed her Ph.D. at the University of Oxford and her undergraduate studies at the University of York. She is interested in the development of social cognition across adolescence; particularly how sociocultural influences may shape its trajectory. Her research spans Western and Eastern regions, including the United Kingdom and China. By adopting a multicultural framework, she hopes to gain a better understanding of the sociocultural factors that may drive social development and affect emotional wellbeing outcomes.

Kathrin Cohen Kadosh
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Abstract
Adolescence is a period of transition, with developmental changes occurring at multiple levels simultaneously (e.g., hormonal, cognitive, neuronal, and socio-environmental). The co-occurrence of these transformational processes could compound risk for mental health problems for a subset of teens, especially towards developing mood and anxiety disorders. In order to progress towards identifying symptoms early and providing age-appropriate interventions, we need to map out trajectories of social-cognitive and affective change and associated neural maturation more comprehensively.

Key Points

- Distinct changes in social behaviour and cognition occur during adolescence.
- Behavioural and cognitive changes in adolescence are accompanied by on-going development in underlying neural networks.
- Age-of-onset data suggest that adolescence is a time of vulnerability for developing anxiety and mood disorders.
- Mapping out typical developmental trajectories can inform the identification of risk profiles.

Adolescence is a period of transition, spanning the years between the onset of puberty and adulthood. It is marked by distinct changes in social behaviour, with parents often reporting familial conflict, preoccupation with peers and heightened emotional responding in their youths. As youngsters move toward adulthood and independence, peer relationships outside the family become increasingly important. Hence, many cues that carry emotional importance for teenagers have been suggested to be interpersonal in nature.[1] Given the substantial changes that take place during this period, it is perhaps not surprising that adolescence is also characterised by a heightened vulnerability for the development of anxiety and mood disorders, as evidenced by age-of-onset data for these conditions.[2] To better understand what underlies these characteristics of adolescence, researchers have begun investigating trajectories of social and emotional development in both healthy youths and youths with emotional and mood difficulties.

A time of vulnerability

Many psychiatric disorders, specifically anxiety and mood disorders such as social anxiety and depression often have their onset in adolescence. Social Anxiety Disorder is a condition characterised by impairing fears of negative evaluation and has a particularly pronounced onset at the juncture to adolescence, with ~90% of cases experiencing impairing symptoms between late childhood and early adulthood.[2] Similarly, prevalence rates for Major Depressive Disorder, characterised by persistent low mood, also increase drastically during adolescence, from 2% in early adolescence to 15% by mid-adolescence.[3]

Systematic biases in how (social) cues in the environment are processed are thought to play a crucial role in the maintenance and possibly onset of these disorders.[4,5] For example, adolescents high in social anxiety have been shown to direct their attention preferentially to social threat in the environment (e.g., threatening faces or words) and interpret ambiguous social situations in a negative manner.[6,7] As social information is often ambiguous (e.g., hearing laughter or whispering from behind you), systematic negative interpretations of these cues may contribute to the maintenance of symptoms by increasing perceived negative social feedback. Similarly, adolescents with increased depressive symptoms have been suggested to process information in a biased way, often attributing negative events to stable, global and internal characteristics of themselves.[8]

Neuroimaging studies comparing functional brain responses between adolescents with elevated social anxiety and/or depression and typically developing youths have confirmed heightened sensitivity to emotionally laden information in the former group. Notably, differential activation patterns and connectivity in brain regions involved in social-emotional responding and emotion regulation have been found in response to anticipated social feedback and socially threatening cues in anxious and depressed teens compared to their healthy counterparts.[9,10,11]

Why is the transitional period of adolescence a time when symptoms of psychiatric

conditions often first emerge? Mental health difficulties in adolescents occur against a backdrop of protracted age-typical changes in social-emotional cognition and behaviour, and associated neural networks. To answer this question, we first need a detailed understanding of typical social-emotional development as the adolescent years unfold – a relatively new field of research.

What is changing in adolescence?

With the onset of puberty, hormonal release sets in motion a cascade of physical developments that result in reproductive competence. Pubertal hormonal changes also affect neural circuitry, including networks linked to social-cognitive and emotion processing.[12] These physical changes are accompanied by psychosocial changes such as increased interest in peer-related cues (e.g., social status and opinions of peers), heightened sensitivity towards (social) reward and engagement in increasingly complex, nuanced interpersonal exchanges, including romantic relationships.[13] Paralleling these physical and psychological developments are important changes in the social environment, too. As children move into adolescence, they face increasing academic demands and societal expectations regarding autonomy and independence. Hence, change happens at multiple levels simultaneously (hormonal, neural, behavioural and environmental), with large individual differences in the rate of change.

In order to measure exactly what and how behaviours, cognitions and neural substrates develop, we need to move beyond anecdotal accounts to data derived from experimental research, i.e., studies that probe social-cognitive and affective processes under controlled conditions. Several such studies indicate continued development across adolescence in social-emotional understanding. For instance, the ability and automaticity with which youths are able to put themselves into another's shoes, i.e. take another person's perspective into account, increases throughout adolescence.[14,15] There is also a growing capacity to engage with others' emotional states.[16] Importantly, these changes happen alongside developments in complex reasoning, learning and reward processing, particularly, but not exclusively, in the processing of social reward.[17]

Changes in the developing brain

In the last two decades, researchers have started to detail the neural bases of these behavioural changes using functional magnetic resonance imaging (fMRI). FMRI allows researchers to study how the human brain responds in a non-invasive manner during a task, and is suitable for use with adolescents and children. Across many different studies and tasks that probe different aspects of social cognitions and emotional responding, researchers have consistently found a set of brain regions involved processing these cues termed the 'social brain network'.[18] This network includes fronto-temporal and also limbic regions including the posterior superior temporal sulcus, temporo-parietal junction, temporal poles, fusiform gyrus, amygdalae and medial prefrontal cortex (see Figure 1 for an illustration). Crucially, these regions correspond to those implicated in differential functioning in depressed and anxious teens.

A growing body of neuroimaging studies attest to protracted functional changes in the social brain network across adolescence in terms of both basic (e.g., processing facial identity or facial emotional expressions) and more complex interpersonal cognitions. However, developmental patterns found across studies have not always been consistent, possibly due to the relatively small sample size used in neuroimaging studies, with differences in age and gender compositions across samples.

With regards to basic social-cognitive skills, the cortical network supporting face-processing abilities (e.g., the fusiform gyrus and the superior temporal sulcus) has been shown to develop continuously across adolescence. For example, Cohen Kadosh and colleagues[19,20] showed that developmental changes in the ability to quickly and accurately process facial identity and emotional expressions are mirrored by the protracted fine-tuning of underlying supporting brain networks.

Beyond studying how faces and expressions are recognised, emotional face stimuli have also been used to study emotional

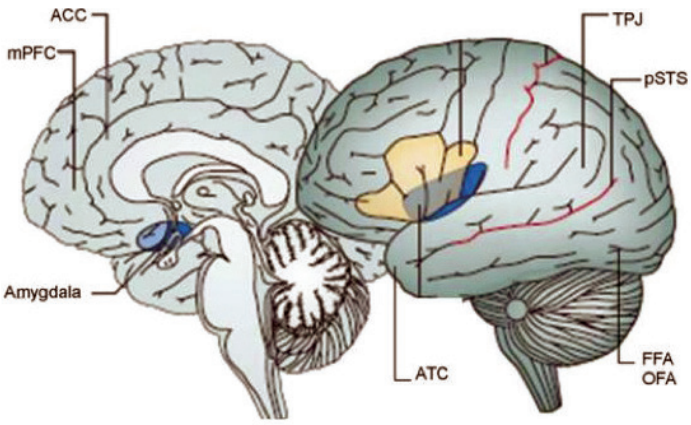

Figure 1: Social Brain Network. Reproduced with permission from Burnett et al.[18] Abbreviations: medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), temporo-parietal junction (TPJ), posterior superior temporal sulcus (pSTS), fusiform face area (FFA), occipital face area (OFA), anterior temporal cortex (ATC) and amygdala.

responses and emotion regulation in adolescents. Interestingly, response profiles of the amygdala (a limbic region involved in fear recognition and learning) to threatening faces across development has been suggested to display quadratic patterns across adolescence, such that there is an increase in emotional responding to these cues from early to mid adolescence, and a decrease towards adulthood.[21,22] However, it is important to note that there are also studies that attest to linear declines from late childhood to adulthood, which suggest that more research is needed to fully understand the developmental changes in this period.[23]

More complex aspects of social cognition, such as emotional responding to social interactions and the regulation of this emotional response, have also been probed using fMRI. Researchers have begun to utilise tasks that are interactive and realistic for adolescents, for example by simulating peer rejection in an online chat room,[24] examining self-consciousness to real-life peer observation via a "Skype-like" camera[25] or reactivity to social media rewards (e.g. "Likes").[26] Results suggest that i) functional responses of social/emotion-processing networks develop at different rates, depending on the region and ii) adolescents often show idiosyncratic activation patterns (i.e., trends are not necessarily linear form childhood to adulthood) in regions involved in reward/threat processing and cognitive/attentional control.

Adolescent-typical changes of increased emotionality and sociability likely serve an adaptive function and increase learning about novel social cues and move adolescents towards independent functioning in society.[27] However, the co-occurrence of several transformational processes could compound the risk for atypical development and mental health problems for a subset of teens.[28] It is plausible that these normative changes in adolescence may 'push' vulnerable youths at the more extreme ends of the spectrum to experience functionally impairing symptoms.[29,30] A central research aim will be to work towards a more comprehensive framework of developmental changes during the adolescent years, which will hopefully provide us with an understanding of how we can detect mental health problems early. This is particularly pressing as early difficulties have been shown to be precursors to persisting mental health problems in adulthood.[31,32]

Conclusion

A plethora of changes in both basic and complex social cognitive processing abilities occurs during the adolescent years. While these may be adaptive, for a subset of individuals, they may increase vulnerability towards developing debilitating mental health disorders. Mapping developmental trajectories would be important for determining what might represent cognitive and neural risk markers for the development of mental health disorders and may inform the development of early interventions.

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Where are we in clinical applications of stem cells in ischaemic stroke?

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Abstract
Safety and feasibility of novel stem cell therapy for ischaemic stroke is emerging from limited numbers of carefully selected patients. Exogenous cell therapy as a means of augmenting brain repair processes is promising supported by favourable outcomes in animal stroke models. Mesenchymal stem cell based trials outnumber neural stem cell trials due to ease of sourcing and administration. Further efficacy evidence from larger numbers of patients remains to be seen.

Overview
Since the discovery of pluripotency and the ability to guide cell differentiation both in-vitro and in-vivo,[1] our understanding of the spectrum of stem cells and their properties has promised therapeutic applications in several neurological diseases, supported in many cases by favourable preclinical studies. Several reviews have discussed the potential indications in stroke, covering the various cell types, time and routes of administration, immunology, preclinical evidence, trial design issues and challenges in the development of clinical applications.[2-4] To date, 19 completed human studies have been reported (Table 1), including a total of 275 stroke patients (range between 5 and 65 individuals per study), and in only 6 of these studies – 142 control subjects. The majority of these studies have been early phase 1 trials with their main objectives being to address safety and feasibility. Seven studies[5-10] have adopted intra-cerebral implantation (IC), three[11-13] have used the intra-arterial (IA) route and nine studies[9,10,14-20] have used intravenous (IV) routes for cell delivery. The average minimum timing of cell delivery was 88 days post stroke, with very wide inclusion criteria ranging from 1 day to 6 years post stroke. Mean (range) follow-up has been 15.2 months (4 to 60 months). The majority of these studies (13/19 studies) have used mesenchymal stem cells (MSCs) of bone marrow origin or bone marrow mononuclear cells (BMMC) (IV,[10,14-20] IA,[11-13] IC8,[10] delivery), two studies used cultured neuronal cells (IC implantation),[6,7] and one study each used neural stem cells (NSC) (IC delivery),[10] neural stem / progenitor (NPC) (IV+IC delivery),[9] foetal porcine (IC) and a cell suspension of neuronal and haematopoietic cells (intra-thecal (IT) delivery).[5]

Neural stem cells
Small trials began in the late 1990s based upon the concept of tissue replacement, something now considered to be a minor and possibly unachievable mechanism of action. In two studies, Kondziolka et al[6,7] used cultured neuronal cells of teratocarcinoma origin. In the first, uncontrolled safety study,[6] non-significant improvement in various neurological scales at six months post implantation and increased relative uptake of fluorodeoxyglucose (FDG) on FDG-PET at the implant site or in ipsilateral adjacent brain was reported. In a further study[7] from the same group improvements in some aspects of neurological function were noted at six months post-implantation compared with an untreated control group although these were not consistent across all neurological assessments. A study of IC implantation of porcine origin foetal cells was terminated due to adverse effects (seizures and cerebral vein thrombosis) not definitely related to cells.[5] Neither of these cell lines has been developed further.

Rabinovich et al[21] reported significant improvement in Karnofsky functional performance status scores among a group of 10 patients who received a sub-arachnoid injection (via lumbar puncture) of cell suspension having immature nervous and haematopoietic (10:1) cells, compared to a control group (no lumbar puncture), at six months post therapy. Qiao et al[9] compared IV MSC with a combination of NSPCs of unspecified foetal origin given IC and umbilical cord derived MSCs given IV in six subjects with stroke and reported improvement in neurological functions and disability levels in the combination therapy group.

The PISCES trial,[10] the first fully regulated study of allogeneic genetically modified foetal NSCs in stroke, was a phase 1 safety and tolerability study in disabled patients six months to five years after stroke, using genetically modified foetal NSCs delivered by IC implantation into the putamen. No cell-related adverse effects were evident up to 24 months, and improvement in some neurological measures was observed. A phase 2 trial is recruiting in the UK at the present (PISCES 2, NCT02117635), investigating neurological effects of IC implantation on arm function change six months after treatment as the primary endpoint.

Table: Published Stroke Stem Cell Trials

Authors	Year	Cell Type	Delivery	Days post stroke	Subjects	Controls	Follow-Up (months)	Key Findings
Kondziolka [6]	2000	Cultured neuronal cells	IC	180-1800	12	0	18	Some functional improvement. No cell related adverse effects. PET scans showed increased uptake at implant site.
Bang [14]	2005	MSCs-Autologous	IV (twice)	<63	5	25	12	Statistically significant improvement in Barthel index, but no effect on mRS and MR imaging. No adverse effects.
Kondziolka [7]	2005	Cultured neuronal cells	IC	360-2160	14	4	6	No significant adverse events. Some functional improvement, but primary outcome was not met.
Savitz [5]	2005	Foetal porcine cells-anti-MHC I antibody pre-treated.	IC	NA	5	0	NA	Terminated by FDA due to significant adverse effects
Rabinovich [21]	2005	Cell suspension-immature nervous & haemopoietic tissue	IT - Subarachnoid	NA	10	Yes	6	No adverse effects reported. Improved functional scores.
Suárez-Monteagudo [8]	2009	MSCs – Autologous	IC	NA	5	0	12	Improvement in neurological condition (details not available)
Barbosa da Fonseca [11]	2010	MSCs (99mTc-labeled)	IA (MCA)	59 to 82	6	0	4	Significantly reduced numbers of grafted cells after 24 h in stroke hemisphere. No significant adverse effects.
Lee [15]	2010	MSCs	IV (twice)	35-49	16	36	60	Improved mRS scores.
Bhasin [16]	2011	MSCs-Autologous	IV	90-360	12	6	6	No adverse effects. FM & mBI increased.
Honmou [17]	2011	MSCs-Autologous	IV	36-133	12	0	12	No adverse effects. Some improvement in NIHSS. MRI reduction of lesion volume by >20% after 1 week.
Savitz [18]	2011	BM MNC-Autologous	IV	1 to 3	10	0	6	No adverse effects. Median NIHSS 13 before and 3 at 6m after cell grafting. Improvement in mRS and BI
Moniche [12]	2012	BM MNC-Autologous	IA	5 to 9	10	10	6	No adverse effects and no improvement in functional outcome.
Prasad [19]	2012	BM MNC-Autologous	IV	7 to 30	11	0	12	n=7/11 had improved on mRS and BI at 6m after therapy.
Bhasin [20]	2013	MSCs-Autologous	IV	30-720	40	0	6	Significant improvement in mBI. No adverse effects.
Qiao [9]	2014	NSPC+MSC	IV+IC	NA	8	0	24	Improvement in NIHSS, mRS and BI. No adverse effects.
Banerjee [13]	2014	MNC- CD34+	IA	<7	5	0	24	improvement in NIHSS and mRS. Reduction in MRI lesion volume
Hess #[10] (Athersys)	2015	Multistem™-Allogeneic	IV	1 to 2	65	61	12	15% of treated group achieved mRS 0-1, NIHSS 0-1 & BI ≥95, compared to 6.6% controls.
Steinberg #[10] (San Bio)	2015	BM MSC-Allogeneic	IC	180-1800	18	0	24	At 1yr significant improvement in NIHSS, ESS, FM. No adverse effects.
Kalladka #[10] (PISCES)	2015	NSC	IC	180-1800	11	0	24	Improvement in NIHSS and Ashworth scores. No adverse effects

#conference proceedings; BI= Barthel Index; BM MNC= Bone Marrow derived Mononuclear cells; ESOC= European Stroke Organization Conference; ESS= European Stroke Scale; FDA= Food and Drug Administration (United States Federal Government Agency); FM= Fugl-Meyer scale; IA= Intra-arterial; IC= Intracerebral; IT= Intrathecal; IV= Intravenous; MRI= Magnetic resonance imaging; MHC= Major Histo-Compatibility; MSC= Mesenchymal stem cells; mRS= modified Rankin Scale; mBI= modified Barthel Index; NIHSS= National Institutes of Mental Health Stroke Scale; NSC= Neural stem cells; NSPC= Neural stem progenitor cells; PET= Positron emission tomography.

Mesenchymal stem cells and bone marrow origin mononuclear cells

Given the more established technology of cell harvest for autologous transplantation and IV administration, bone marrow-derived mesenchymal stem cells (MSCs) and a less well characterised population of bone marrow mononuclear cells (only some of which are stem cells) have been the most frequently investigated in both preclinical and clinical studies to date. In animal studies, there is evidence of functional improvement, reduction in infarct volume, and systemic immunomodulatory effects (predominantly from acute administration within hours or days of induction of ischaemia), but IV administered cells neither engraft nor enter the brain in detectable numbers, indicating a paracrine or trophic effect. Intra-arterial (IA) administration delivers more cells to the brain but persistence is also limited,[22] and IA delivery has been

associated with more complications due to embolic stroke, presumably secondary to cell clumping, and necessitating careful modification of cell delivery protocols. Clinical studies are limited, but in humans, two months after stroke, IA administration of autologous bone marrow CD34+ cells[11] labelled with Technetium-99 m showed transient distribution to brain at two hours post-delivery but persistence of signal in only 2/6 patients at 24 hours. Intravascular delivery is therefore unlikely to represent an engraftment strategy, and both animal and human studies have adopted a "neuroprotectant" paradigm for investigation.

Both bone marrow and other sources of MSCs (eg adipose tissue or umbilical cord blood) may also be used as allogeneic therapies, potentially circumventing one of the major drawbacks of autologous cell therapy, the delay incurred in laboratory characterisation of specific cell populations, and even greater delay involved in ex-vivo culture expansion – a particular issue when acute delivery within plausibly neuroprotectant time windows appears to be the likeliest relevant treatment paradigm. Average time to therapy from marrow aspiration was six days (range 0.37 to 9 days) among 17 myocardial infarction trials.[23] Such autologous approaches also face the possible drawback of wide variations in dosing, since cell yield is unpredictable and varies among individuals, for example as seen in the study of Bang et al[14] using ex-vivo culture-expanded autologous MSCs delivered IV in post-stroke patients. Trial design for autologous cells is further compromised by the ethical and logistical difficulties of undertaking blinded control studies, although this has been achieved in other disease areas such as cardiology. Autologous bone marrow derived MSCs have also been delivered by IC implantation in a single centre early phase study of five subjects.[8] Autologous BMMC12 with early IA administration (five to nine days after stroke) showed no safety issues. From 2010 to 2015 seven further studies using IV delivery have reported no safety issues. Four[15-17,20] of these studies have relatively delayed (30 to 720 days) cell administration compared to three[10,18,19] other studies which have administered cells within the first week post stroke. Follow-ups have ranged from 6-60 and 6-12 months respectively.

The great majority of studies report improvements in the treated group in a variety of functional measures including National Institutes of Health Stroke Scale, Barthel Index of activities of daily living, and the modified Rankin Scale between three and six months post therapy, but trial inclusion criteria are generally very broad, and control groups absent, so claims of efficacy are not yet supported by evidence. At best, it is possible to conclude that no major cell-related safety issues have been reported to date, although with the caveat that there have been a wide range of cell types used and follow-up reports are generally short term.

The largest multicentre study to date in stroke has been that of Hess and colleagues, using allogeneic cells from a donor bone-marrow derived cell line ("Multistem") characterised as multipotent adult progenitor cells (MAPCs) that have been depleted of CD45 (+)/glycophorin-A (+) cells. The trial included 126 subjects (65 patients given MAPCs and 61 placebo control subjects) delivered IV within 24-48 hours of stroke onset. A trend towards better functional outcomes in the MAPC group has been presented, based on the subset of control subjects recruited within 36h. Consistent with MSC's pre-dominant anti-inflammatory effects in general, in the treated group, two days post administration, significant lower level of circulating CD3+ T-cells were observed, suggesting a reduction in the inflammatory response post-stroke.

Mechanisms of Action

Early embryonal stem cell (ESC) work focussed on cell engraftment and replacement as prime concept for neuro-restoration. Other mechanisms that are now widely investigated include concepts of stimulating endogenous brain remodelling in particular angiogenesis, neurogenesis, favourable gene expression and axonal restoration and paracrine effects of modulating post-stroke inflammation. The different routes of administration of stem cells dictate and/or limit certain actions. Detailed review is out of scope and has been published elsewhere.[2,3] The neural stem cells in the sub ventricular zone of the adult human brain proliferate and differentiate in response to focal ischaemia and can potentially be stimulated by injected NSCs. Angiogenesis is key to maintaining neural proliferation and both NSCs and MSCs have been known to stimulate angiogenesis to varying degrees. Although stroke limits axonal sprouting, NSCs and MSCs have shown to promote growth factors to improve sprouting, increase axonal density and downregulate inhibitory proteoglycans. Oligodendrocyte numbers are observed to increase which help remyelinate new or damaged axons. Uncontrolled inflammatory response can be deleterious but when controlled can help with repair and the ability of stem cells to modulate host inflammatory microenvironment has been observed resulting in favourable functional outcomes in animal models.

Next Steps

A large European multicentre randomised, placebo-controlled, double blind trial to investigate the efficacy of IV allogenic adipose derived MSCs (RESSTORE) has been funded and will commence recruitment in the coming months.[24] A UK multicentre open-label phase II study[25] of intracranial administration neural stem cells (PISCES-2) in subacute stroke is currently recruiting with the primary aim to determine the possible relationship with functional recovery of a paretic arm, measured by the action research arm test. Further trials of MAPCs are planned, and a large number of small, predominantly single-centre studies of IV autologous cells are registered on international clinical trials sites.

Conclusions

Concepts of the potential mechanisms for cell therapy in stroke have moved substantially over the past 5 years, away from a paradigm that envisioned cell engraftment and replacement (albeit a mechanism still potentially relevant, if minor, for intracerebral implantation) and towards a view of cells as a stimulant for endogenous recovery processes and modulator of immunological and inflammatory changes after stroke. Intravascular delivery in particular has more in common with neuroprotectant approaches and this increasingly informs trial design. Investigation of stem cell therapy in stroke remains in early phase trials. The widely different populations of cells that are termed "stem cells" may have very different properties and should not be considered as homogeneous. Several phase II/III trials that are ongoing or planned will refine clinical trial paradigms and pave the way for definitive trials.

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Recent advances in narcolepsy

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Abstract
Narcolepsy is thought to affect 0.05% of Caucasian populations and frequently causes severe symptoms across the 24-hour period. It is best viewed as a disorder of sleep-wake regulation with particular abnormalities of the rapid eye movement (REM). Typical cases are due to specific loss of a subset of hypothalamic neurons containing the neuropeptide, hypocretin (orexin). Several lines of evidence, including a causal link to the swine 'flu vaccination, suggest autoimmune destruction of these neurons as an initial event.

Narcolepsy is now classed as either type 1 or type 2, depending on sleep investigation results and whether cataplexy and/or hypocretin deficiency is present. However, it is likely the classification system will be further refined.

Treatment options remain symptomatic and are often only partially effective. A new wake-promoting agent that increases brain histamine levels (pitolisant) has recently become available and will probably be used alongside modafinil and more traditional psychostimulants such as dexamphetamine. Powerful hypnotic agents, notably, sodium oxybate, consolidate the fragmented sleep frequently seen in narcolepsy and improve many of the daytime symptoms as a likely consequence.

Key Points

- The narcoleptic syndrome is best viewed as a disorder of sleep-wake regulation, particularly affecting the REM sleep stage. Its phenotype is wide and includes elements not directly related to sleep such as appetite control, perhaps reflecting hypothalamic dysfunction.
- Nocturnal sleep fragmentation is a key feature and helps to explain why the sedative agent, sodium oxybate, is the best available treatment.
- The most recent diagnostic classification divides narcolepsy into type 1 (with cataplexy and significant hypocretin deficiency) and type 2 (without cataplexy and normal or low hypocretin levels). In these latest guidelines, the multiple sleep latency test remains an important diagnostic tool despite its poor sensitivity and reliability.
- A recent surge in incidence amongst children in particular following the swine 'flu vaccination (Pandemrix) in 2009 has fuelled the notion of an autoimmune aetiology although many questions remain.
- Future treatments are likely to focus on hypocretin replacement via oral or intra-nasal medication. The newest useful treatment to become available is a novel stimulant drug that increases cortical histaminergic transmission, Pitolisant.

Introduction

Despite major advances in our understanding of narcolepsy and its neurobiology over the last 15 years, many questions concerning its nature and causation remain. Furthermore, the remarkable landmark discovery that specific loss of around 70000 neurons in the lateral hypothalamus containing the neuropeptide hypocretin could cause human narcolepsy and cataplexy[1] has yet to lead to any significant therapeutic breakthroughs. Nevertheless, study of the hypocretin system in the brain has provided significant insight into how the sleep-wake cycle is regulated as well as furthering the diagnostic process in narcolepsy.

Given that narcolepsy reflects a neurochemical deficiency with a presumed spectrum of severity, perhaps it is not surprising that narcoleptic symptoms also vary between patients. In general, however, the adverse effects of narcolepsy on quality of life are increasingly recognised and most patients have equivalent measures of disability to those with treatment-resistant epilepsy.[2] Moreover, narcolepsy typically affects young subjects, is life-long and also associated with numerous co-morbidities.

Promising research in several animal models of narcolepsy suggests that pharmacological replacement of hypocretin as a specific and effective pharmacological treatment remains a viable goal.

Defining the narcoleptic syndrome

Narcolepsy is now best viewed as a syndrome of severe sleep-wake dysregulation, particularly with respect to rapid eye movement (REM) sleep (Figure 1).

Although small in number, excitatory hypocretin-containing neurons project to numerous key brain areas crucial for behavioural state control. Without these neurons, the brain is far less able to maintain or consolidate either full wakefulness or, indeed, the state of sleep. Subjects may spend significant portions of the day somewhere in the spectrum between wake and sleep with reduced alertness or concentration as major features. Study of narcoleptic patients has furthered the concept of "localised" sleep, occurring independently in discrete parts of the brain. Indeed, elements of normal REM sleep intruding into the predominantly wakeful state, such as bizarre visual imagery or voluntary muscle paralysis, are key clinical diagnostic features for narcolepsy.

Cataplexy remains by far the most specific symptom in narcolepsy and affects around 70% of subjects. The wide spectrum of symptom severity is increasingly acknowledged with some patients reporting simply an inability to

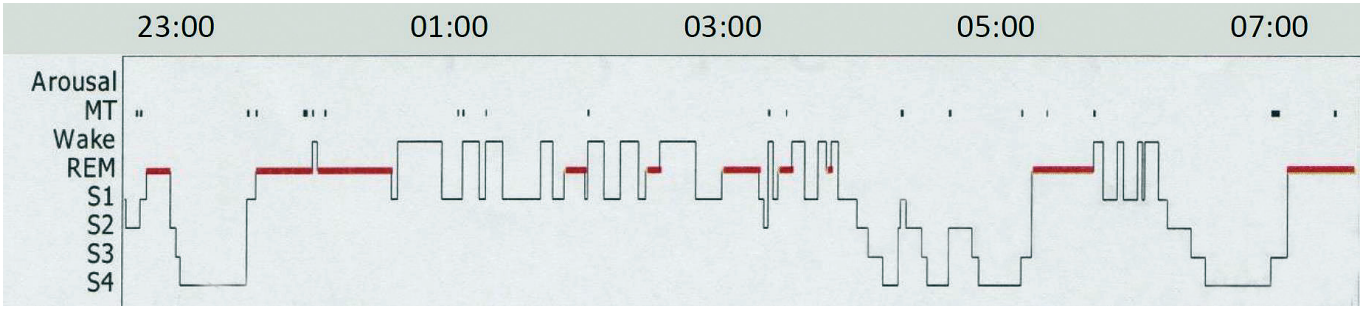

Figure 1: An example of a hypnogram that demonstrates the typical features of poor overnight sleep in severe narcolepsy. Time through the night is shown at the top. The sleep architecture is both severely fragmented and dysregulated. The subject enters REM sleep (red bar) abnormally quickly, within 10 minutes of sleep onset, and thereafter has numerous awakenings from REM sleep, explaining the reported experience of numerous disturbing and vivid dreams. Furthermore, significant body movement is seen within REM sleep episodes correlating with likely dream enactment (REM sleep behaviour disorder). An unusual distribution of deep non-REM sleep (S3 and S4) persisting late into the night is seen. In normal subjects, deep non-REM sleep usually all occurs within the first third of the sleep period. MT – movement time; S1,S2,S3,S4 – progressively deeper stages of non-REM sleep.

deliver punchlines of jokes with apparent speech arrest. Precisely why emotions or their anticipation should trigger neural activity in descending (glycinergic) pathways inhibitory to motor neurons, a feature of normal REM sleep, remains a fascinating conundrum. Cataplexy in children is now recognised as often having a distinct phenotype to the adult form. In particular, localised facial weakness is more apparent, often accompanied by grimacing, tongue protrusion or other "positive" motor phenomena which may lead to diagnostic confusion.[3]

Prior to changes in the latest diagnostic guidelines (International Classification of Sleep Disorders, ICSD-3),[4] it was possible to diagnose narcolepsy on clinical grounds alone if typical cataplexy was present in the presence of persisting daytime somnolence. However, investigations are now required for formal diagnosis and distinction is made between type 1 and type 2 narcolepsy (see Table 1).

The emphasis on the multiple sleep latency test (MSLT), especially in type 2 narcolepsy, has led to major concerns, given its poor diagnostic sensitivity and specificity. Furthermore, it is a test very prone to protocol violations and associated difficulties with interpretation such that many clinicians would argue narcolepsy without cataplexy, in particular, should remain predominantly a clinical diagnosis, perhaps supported by investigations. Some evidence is emerging that partial hypocretin deficiency may explain many cases of type 2 narcolepsy.[5]

A number of symptoms and medical issues not obviously or directly related to sleep are now recognised in narcolepsy. Many patients have dysregulation of appetite control and admit to severe food cravings, usually at night particularly for sweet flavoured items. Not infrequently, nocturnal eating occurs without conscious control or full awareness as an apparent non-REM sleep parasomnia that may accompany narcolepsy. As a possible consequence of disordered appetite control, rather than reflecting relative physical inactivity, obesity is significantly commoner in narcoleptic populations even though evidence suggests they eat less per day than control populations.[6] Whether this reflects a metabolic disorder, perhaps related to abnormal control of hypothalamic satiety hormones such as leptin, remains to be established. Similarly, although poorly studied, narcoleptic subjects also often report marked postprandial sleepiness, particularly after large unrefined carbohydrate meals. Manipulations of diet can therefore sometimes help improve general alertness.

Male narcolepsy patients, in particular, who put on significant weight in middle-age are at significant risk of obstructive sleep apnoea syndrome (OSAS) which further complicates their sleep-wake control. Deteriorating control of daytime sleepiness in an obese subject, previously well controlled with daytime stimulant therapy, might suggest this additional sleep disorder. Unfortunately, even if correctly diagnosed with OSAS, narcolepsy patients tend to tolerate ventilation masks very poorly, often due to dream-like

Table 1: New diagnostic criteria for narcolepsy from the International Classification of Sleep Disorders (ICSD-3)

Narcolepsy
The subject must have periods during the daytime in which there is an irrepressible need to sleep or actual lapses into sleep, occurring for at least three months

Type 1 Narcolepsy	Type 2 Narcolepsy
Narcolepsy with cataplexy and/or hypocretin deficiency	Narcolepsy without cataplexy
The presence of one or both of the following:	All 4 of the following criteria must be met:
1. typical cataplexy and a mean sleep latency of ≤8 minutes with 2 or more sleep onset REM periods (SOREMPs) seen on a MSLT (i.e. REM sleep occurs within 15 minutes of sleep onset) performed according to standard techniques	1. a mean sleep latency of ≤8 minutes with 2 or more sleep onset REM periods (SOREMPs) seen on a MSLT performed according to standard techniques
note : a SOREMP on the preceding nocturnal PSG (i.e., REM onset within 15 minutes of sleep onset) may replace one of the SOREMPs on the MSLT.	note : a SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT.
2. CSF hypocretin-1 concentration, measured by immunoreactivity, is less than 110 picograms/ml or <1/3 of mean values obtained in normal subjects with the same standardised assay.	2. typical cataplexy is absent.
	3. either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is >110 picograms/ml or >1/3 of mean values obtained in normal subjects with the same standardised assay.
	4. the hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnoea, delayed sleep phase disorder, or the effect of medication or substances, including their withdrawal.

ICSD-3 now recognises a pathophysiological subtype:

• narcolepsy type 2 due to a medical condition: all criteria are met for narcolepsy type 2 PLUS a disease likely to be responsible.

Potential conditions included are: Parkinson's disease; myotonic dystrophy; tumours or infiltrative disorders such as sarcoidosis involving the hypothalamus; autoimmune or paraneoplastic conditions with anti-Ma-2 or anti-aquaporin-4 antibodies; multiple sclerosis; Prader-Willi syndrome; and head trauma.

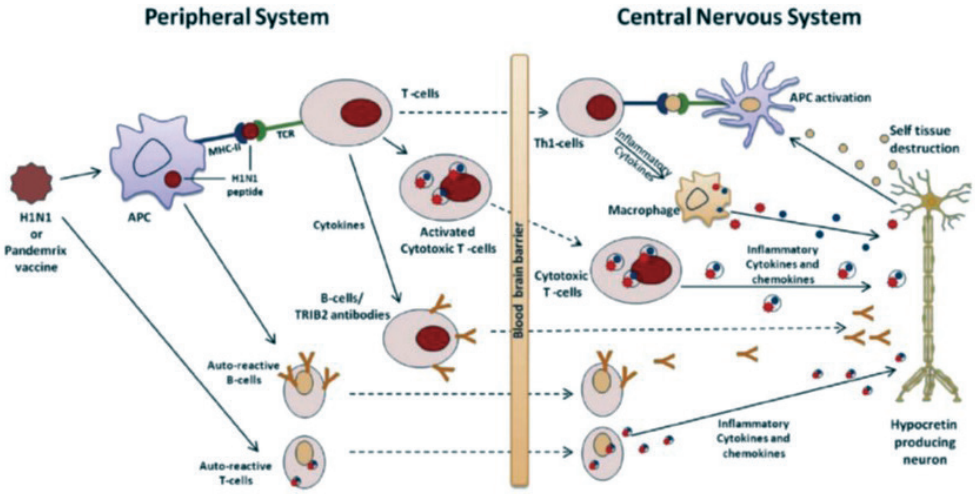

Figure 2: Potential mechanisms for narcolepsy onset following Pandemrix vaccination or H1N1 seasonal infection. Stimulation of auto-reactive T-cells or B-cells potentially target hypocretin producing neurons via at least 5 different pathways : 1. Molecular mimicry of T-cells describes the activation of cross-reactive T-cells that recognise an H1N1 epitope which then migrate to the CNS where cross-reactivity occurs with an antigen specific to hypocretin producing neurons. Resulting cytokine and chemokine release activates macrophages which mediate tissue damage. Subsequent release of hypocretin self-antigen potentially perpetuates the process. 2. H1N1 antigens or Pandremix vaccine may cross-link the MHC and TCR molecules independent of antigen specificity, activating cytotoxic T-cells which are auto-reactive and specific towards hypocretin producing neurons. 3. Although thought less likely, molecular mimicry involving B-cells and antibody mediated disease could also be involved, possibly targeting so-called TRIB2 as a cross as a cross-reactive antigen. This would require signals from activated T-cells. 4. Bystander activation of B-cells as a result of general immune activation. 5. Bystander activation of T-cells as a result of general immune activation. APC: antigen presenting cell; CNS: central nervous system; H1N1: N1N1 influenza A virus or epitopes from adjuvant vaccine; MHC: major histocompatibility complex; TCR: T-cell receptor; TRIB2: tribbles homologue 2.

or hallucinatory intrusions involving the mask itself. If so, additional nocturnal sedation may allow better compliance.

It seems very likely that mood disorders are much commoner in narcolepsy patients both as a likely reaction to the disruptive effects of the syndrome and the accompanying features of sleep deprivation. The input of psychiatric expertise can therefore be useful although, in the author's experience, care must be taken not to interpret REM sleep-related phenomena, particularly hypnagogic hallucinations without a delusional component, as primary psychotic features.

Generalised pain syndromes resembling fibromyalgia are often a prominent concern in narcolepsy patients. The bi-directional relationship between sleep disruption and pain perception may largely explain this observation.[7] Neuropathic pain agents such as gabapentin are generally more useful than routine analgesics and much preferred to opiates which invariably disrupt the sleep-wake cycle and control of nocturnal breathing. Restless legs syndrome also appears particularly severe in some patients and may merit specific therapy with low dose dopaminergic agonists, especially if associated periodic limb movements are prominent overnight.

Theories of causation

The fact that typical type 1 narcolepsy has one of the tightest HLA associations of any disease has fostered theories of an autoimmune aetiology for some time even though there are no clear links to other autoimmune conditions. Over recent years, however, a number of associations with presumed pathogenic antibodies have been proposed without clear subsequent substantiation.[8] A reliable relationship to T cell receptor polymorphisms in narcoleptic patients has suggested that cell mediated destruction of hypocretin neurons may be an important mechanism behind cell death.[9] Disappointingly, attempts to treat narcolepsy with various immunomodulatory agents have generally been unsuccessful in the absence of controlled trials. A recent case report suggesting an impressive clinical response to a monoclonal antibody, prescribed for an incidental lymphoma, is intriguing, however.[10]

Evidence from several countries that the swine 'flu vaccine, Pandemrix, given to several million people in 2009 and early 2010 led to an abnormal surge in childhood and, to a lesser degree, adult cases of typical narcolepsy has further fuelled the "autoimmune" theory. If correct, however, it remains unclear whether the pathogenic process reflects a reaction to the strong adjuvant chemicals added to the vaccine or is simply molecular mimicry, related to proteins within the vaccine or indeed the virus itself. Equally unexplained is the frequent considerable delay between any proposed vaccine-related inflammatory reaction in the hypothalamus and narcolepsy symptom onset. One speculative theory is that any initial minor damage to the hypocretin neurons may promote a subsequent slow degenerative process, perhaps by an excitotoxic mechanism given the extremely high metabolic energy demands of these particular neurons.

Further insight into the potential vulnerability of hypocretin neurons is likely to come from a rare autosomal dominant genetic disorder reported in several families with a DNMT mutation.[12] Although the phenotype is a little variable, particularly regarding symptom severity, many affected individuals have typical narcolepsy type 1 with cataplexy and associated hypocretin deficiency as part of their clinical picture. Other features may include myoclonus, deafness, ataxia and cognitive decline, superficially resembling a mitochondrial disorder and perhaps supporting an explanation of specific neuronal damage in neurons with particularly high energy demands

New and future treatments

Delays both in the diagnosis of narcolepsy, often years after symptom onset, and any significant loss of hypocretin neurons after an initial putative immune-related insult mean that standard immunosuppressive therapy is unlikely to be effective or practicable. The future realistic goal for more effective treatment probably lies with hypocretin replacement, ideally via an oral agent. To date, rodent and canine models of narcolepsy due to hypocretin deficiency or receptor mutations have demonstrated good responses to a variety of techniques that increase brain levels of hypocretin, fuelling hope for the human condition.[13] Unfortunately, hypocretin's neuropeptide structure makes it difficult to develop oral agonists that will penetrate into the brain although effective oral antagonists have been produced as treatments for insomnia. Intra-nasal hypocretin has produced promising data in sleep-deprived primates but the clinical data relating to narcolepsy has been disappointing so far.

The conventional approach to narcolepsy treatment is to prescribe daytime psycho-stimulants that are thought to activate the catecholaminergic component of the ascending reticular activating system. These drugs may suppress cataplexy in addition to improving daytime alertness although agents to suppress REM sleep, typically anti-depres-

sant drugs such as venlafaxine, may be needed to treat the former. Modafinil with or without supplemental amphetamine or amphetamine-like drugs, such as methylphenidate, would be a typical wake-promoting combination. These agents are thought to have a dopaminergic action, either directly or indirectly, although Modafinil's precise mechanism remains obscure, despite having been used as a first-line therapy for 17 years. A newly developed psychostimulant with a novel mode of action on central histaminergic systems is likely to become a useful additional agent to improve daytime alertness.[15] Around 70000 histaminergic neurons in the anterior hypothalamus exert a powerful cortical excitatory effect that promotes wakefulness via H1 receptors. Histamine activity correlates well with the active or wakeful state and is generally lower than normal in narcolepsy. Pitolisant is a selective histamine antagonist which inhibits H3 autoreceptors in the hypothalamus, effectively promoting cortical histamine release. The drug has recently gained approval and early experience suggests that it will be a useful addition to currently available stimulant therapy.

Over the last decade, increasing attention to improving overnight sleep in narcolepsy has produced significant therapeutic advances. In particular, the controversial drug, sodium oxybate, usually given in divided doses overnight has been shown by trial data and in clinical practice to be the most effective single drug available.[14] Aside from consolidating nocturnal sleep and enhancing its deeper stages, sodium oxybate often abolishes cataplexy within a few months of use as well as significantly improving daytime somnolence. Given its high price, issues over cost effectiveness have unfortunately severely limited its availability as have concerns over its potential misuse in society, primarily as a "date rape" drug.

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Burden of hospitalisation in MS: How the MS Academy will support service change

Sarah Gillett, Managing Director, Neurology Academy

A report jointly published in November 2015 by NHiS Commissioning Excellence and the Multiple Sclerosis Trust (Thomas et al. 2015) highlights for the first time the burden that unplanned hospital care for people with multiple sclerosis (MS) places on the NHS. It vital that we explore how services for people with MS can be improved, because anecdotally we know that people with MS may not be receiving the services they need, and this is now backed up by the report's analysis of Hospital Episode Statistics. Current failures to adequately support patients leads to unnecessary emergency hospital admissions, which could be prevented if a more proactive approach to MS management were adopted.

Measuring admissions

Approximately 90,000 people in England live with MS, and the period between 2009 and 2014 saw a steady increase in admissions to hospital. Whilst a large proportion of the elective admissions in MS will be due to the administration of disease modifying drugs (DMDs), the non-elective admissions are mainly a result of a problem arising.

In the year 2013/14 there were 23,554 emergency admissions for people with MS which cost the NHS £43 million. Despite emergency care being the minority of the total admissions into hospital, these admissions consume a disproportionately large amount of the overall admissions costs. In 2013/14 only 27% of admissions for people with MS were non-elective, but these accounted for 46% of hospital care costs.

Of the 23,554 emergency admissions recorded these relate to only 14,960 unique individuals (17% of all the people with MS in England) and demonstrate that many of these emergency admissions were re-admissions. This means 37% (8,695) people are hitting the 'revolving door' of A&E.

Reasons for admission

Why were people with MS being admitted to hospital? Headline results from the report reveal that the most common reasons for emergency admissions were preventable problems like urinary tract and respiratory infections, constipation and MS itself (including MS relapse). Bladder and bowel problems alone cost the NHS £11million among MS patients in 2013/14, whilst respiratory infections totalled in excess of £5.5 million.

Supporting MS service development

It is information like this that supports the Neurology Academy to define what areas clinicians undertaking the MS MasterClass training should focus on for their inter-module projects.

An integral part of the MasterClass programme, which has been honed over the last 14 years, is the inter-module project. Neurologists utilise the skills and knowledge they have gained during the taught sessions by undertaking a project or in some cases a service audit within their own trust to examine local service performance. By doing this they establish how services are functioning and work on more proactive care management strategies for patients. Ultimately this leads to better services for patients, and by addressing the problems identified often reduces overall service costs.

Data intelligence from the report highlights potential areas for delegates to investigate, such as urinary tract infections (UTIs), which accounted for 14% of all emergency admissions of people with MS in England in 2013/14 and on average cost £2,556 per admission. Rates of UTIs in MS are worryingly high compared to the rate of emergency admissions for a UTI amongst the general population, which is under 3%. Infections are also known to aggravate the symptoms of MS and could potentially exacerbate an MS relapse so should be a real focus for action.

By MS MasterClass delegates turning their attention to UTI, and issues like it, which seriously affect the wellbeing of MS patients, the inter-module project will in many cases become the catalyst for implementing new strategies that support local service improvement. Our hope is that real change for people with MS will stem from the Academy's innovative training programme. www.msacademy.co

Download a copy of the report "Measuring the burden of hospitalisation in multiple sclerosis: A cross-sectional analysis of the English Hospital Episode Statistics database 2009-2014" at: http://www.nhis.com/commissioning-excellence/ms-report

Public and patient involvement (PPI) at King's: Community for Research Involvement and Support for people with Parkinson's (CRISP)

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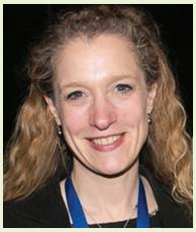

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Liba Stones
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Author details continued overleaf

Introduction

The concept of patient and public involvement (PPI) in healthcare has been around since 1974, however it has been a struggle for it to be effectively implemented and supported,[1] as evident from several organisations set up and abolished over time (Table 1).[2] Specific to health research, PPI has recently become a popular notion and as such is the standard expectation of most government funded health research. The need to increasingly hold researchers to account, recognise barriers in knowledge and research, and occasionally, the unrealistic expectations, have dominated research regulations.[3,4] Therefore, there has been a growing requirement to give patients and the public the ability to contribute and shape research.[5,6] This increase in PPI allows for greater quality reassurance and provides the certainty that the research being conducted will be beneficial for making the concept of bench-to-bedside a reality.[7,8]

The Health Research Authority (HRA) in the UK conducted a survey on public attitude towards medical research in which they found patients would have greater confidence in research if they had counselled the design and implementation of the research study.[9] Many patients are well equipped with understanding their own condition through experience, sometimes, better than the clinicians and researchers. Therefore, their ambitions and viewpoints may not have been considered by those conceptualising research for their condition. By having PPI in active partnership with the researchers and clinicians, a unified research design is achieved which is likely to have beneficial effects on patients and the National Health Service (NHS). This is echoed by the Research Ethics Committee (REC) who are often concerned by the patient specific aspects such as consent, recruitment and information quality, much of which can be addressed by a PPI group.[10] A few core fundamental aspects of having a PPI in research are that it will help:[11,12]

(a) Corroborate the relevance of the project to the patients;
(b) Improve the basic research question;
(c) Identify appropriate research methodologies;
(d) Understand the potential outcomes for patients;
(e) Achieve greater understanding of how to enable the research to deliver to time and target (i.e. recruiting patients in research period).

NIHR Initiatives

The National Institute of Health Research (NIHR) work to provide support and guidance to researchers in various ways to deliver practical research, which works to make patients and the NHS better.[13] One of the aims of NIHR is to empower patients and the public to participate and shape research,[14] hence, they fund an advisory group, INVOLVE. This group is one-of-a-kind in the world, and works to collate expertise and experiences in research through increasing public involvement.[15] INVOLVE are defined as a group aiming for research to be carried out 'with' or 'by' the public rather than research 'to', 'about' or 'for' the public.[16] The NIHR has set out various PPI guidelines with the aim of ensuring researchers involve the public in their studies as much as possible, hence

Table 1: Brief summary of PPI set up in NHS (England)

1974	Community Health Councils (CHCs) set up
2000	Overview and Scrutiny Committee set up
2002	CHCs abolished
2003	Commission for Patient and Public Involvement in Health (CPPIH)
2003	Patient Advice and Liaison Service (PALS), Independent Complaints Advocacy Service (ICAS), and Patient and Public Involvement Forums (PPIfs) set up
2004	CPPIH abolished
2006	PPIfs abolished
2006	Local Involvement Networks (LINks) set up
2013	LINks abolished
2013	Healthwatch England set up

Clare Meachin
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He is the medical director of the National Parkinson Foundation International Centre of Excellence at King's College, London. He sits on the Nervous Systems Committee of UK Department of Health, National Institute of Health Research and also serves as co-chairman of the appointments/liaison committee of the International Parkinson and Movement Disorder Society (IPMDS) and is currently serving as the member of the scientific programme committee of the IPMDS. He is the Chairman of the IPMDS Parkinson's disease (PD) non-motor study group. He serves on the task force of practice parameter group for PD and restless legs syndrome (RLS) and more recently Non-Motor Symptoms of Parkinson's, American Academy Neurology. He is the Editor in Chief of Nature Parkinson's disease journal and the European Editor of Basal Ganglia and is in the editorial board of Parkinsonism and Related Disorders and Journal of Parkinson's Disease.

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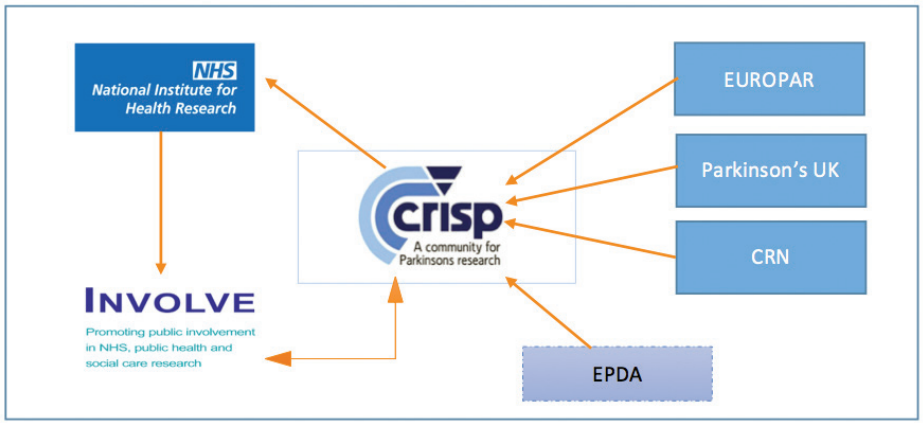

Figure 1: CRISP follows the principles set by INVOLVE. INVOLVE is funded and run by the NIHR. CRISP works closely with EUROPAR (a non-profit multi-displinary organisation with key opinion leaders working to improve Parkinson's related clinical research), Parkinson's UK (a supportive research charity), members of the CRN sit in CRISP as representatives, and the EPDA supports the overall aims of CRISP.
CRISP, Community for Research Involvement and Support for people with Parkinson's; EUROPAR; EUROpean Network for PARkinson's Disease; UK, United Kingdom; CRN, Clinical Research Network; EPDA, European Parkinson's Diease Association.

safeguarding the practicality of the research outcome. As a result, INVOLVE sets out detailed guidelines for researchers to follow ensuring the successful achievement of PPI.[16]

The importance of PPI in research is evident in all stages of submitting project proposals and up to the final report. This is echoed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), which manage the NIHR, Evaluation, Trials and Studies (NETS) programmes, who expect there to be active PPI in any research they fund and support.[17]

What is the impact of PPI?

A review into the impact of PPI has been undertaken by Staley (2009) who reported there being a significant effect on the identification of the research question to the design and delivery of the project.[18] Staley also finds early involvement to be beneficial for cost and ethical difficulties which may later arise. Their review highlights that the impact of PPI has no robust method of evaluation. Nonetheless, the general opinion is that PPI has a positive impact on research in almost all aspects. Brett and colleagues (2014) conducted a review of the impact PPI have on research whereby they found PPI helped identify researcher's limitation in knowledge, which equipped them to then develop to resolve these problems. Alongside these practical benefits of having PPI, they have also been shown to have financial benefits by helping to prevent potential losses through helping refine and identifying pitfalls in projects during the design stage.[6,19,20]

> *"...attending these meetings allows me to hear a patients perspective and experience of my clinics which is very helpful as I can then go back and make appropriate changes to further help my patients..."*
>
> *Miriam Parry (Specialist PD nurse, CRISP)*

Several studies have shown successful design and implementation of research, following PPI group advice, which provided vital information to conduct successful research.[21-27] INVOLVE, along with the Mental Health Research Network (MHRN) and the School for Primary Care Research, commissioned case studies looking at research and PPI,[28-32] and found a significant positive impact of PPI.

Whilst PPI is certainly not a new model, as evident from mental health research utilising PPI involvement for decades now, it is not as well-established in all specialties. Neurodegenerative conditions, such as Parkinson's disease (PD), are set to rise 28% by 2020[33] creating a substantial need to perpetuate research in this field. Hence, the need for robust PD PPI has been an unmet need for some time, however, this is now changing.

Local Initiative at King's translating to a national project

King's College Hospital (King's) Parkinson's Centre led the development of the 'King's PPI group', which consisted of a range of public representatives (patients, carers) and NHS trust staff (researchers, health professionals) as well as representation from key PD patient charities (see Image 1). The original members of King's PPI were approached following a movement disorder multidisciplinary team meeting at the trust. Potential patients where asked if they

Image 1: CRISP meeting
Left to right: Eros Bresolin (PwP), David Charlton (PwP), Alexandra Rizos (EUROPAR European Research manager), Lauren Perkins (Senior research coordinator), K Ray Chaudhuri (Prof of Movement Disorders at King's), Miriam Parry (Specialist PD nurse), Theresa Chiwera (Research nurse), Stephen Roberts (PwP), Rosalind Roberts (carer of PwP), and Flora Hill (carer of PwP).

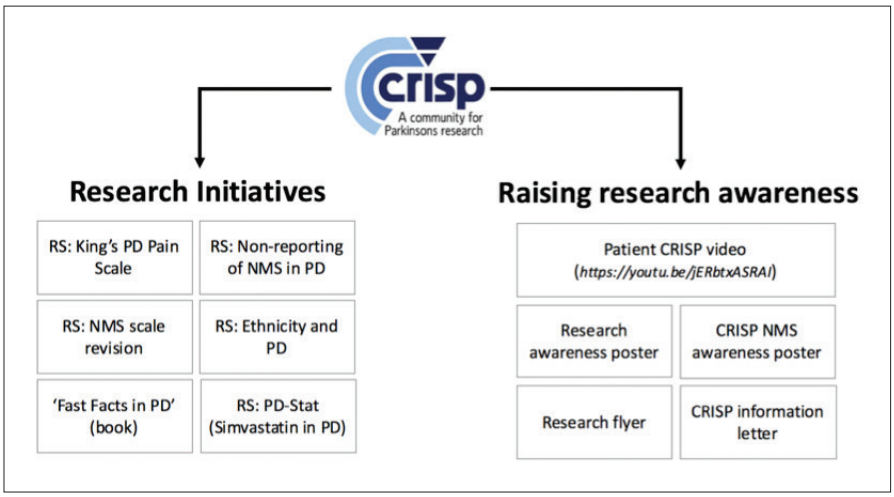

Figure 2: CRISP main two aims; Parkinson's research and raising patient participation awareness
PD, Parkinson's Disease; RS, research study; NMS, non-motor symptoms; CRISP, Community for Research Involvement and Support for People with Parkinson's; Stat, simvastatin.

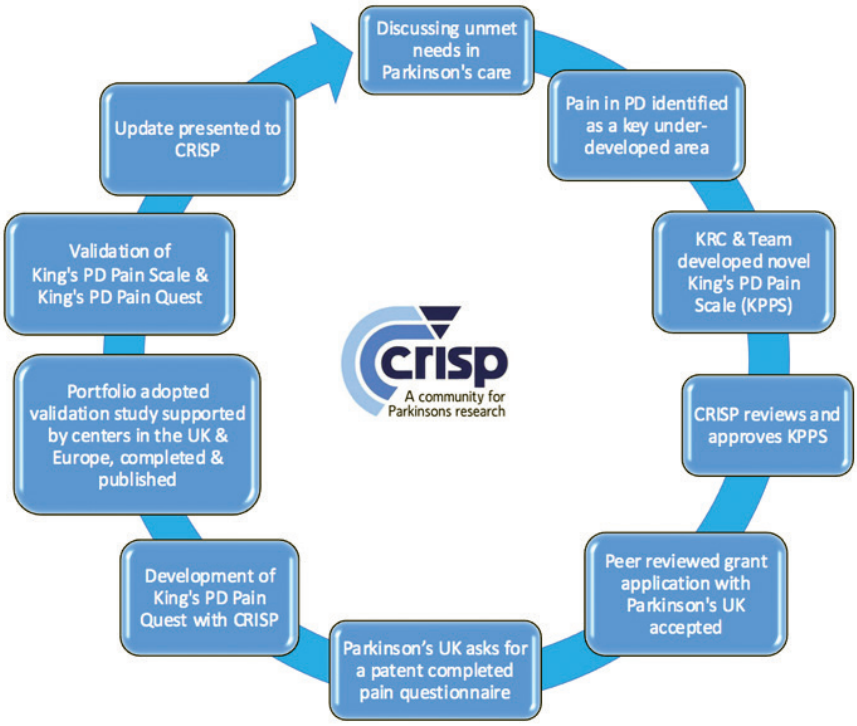

Figure 3: Flow-chart representing CRISP involvement in developing the King's Parkinson's Disease Pain Scale (King's PD Pain Scale). During CRISP meetings and prior research, the issue with the inability to identify and help PD patients with pain was recognised as an underdeveloped problem. The researchers developed a novel PD Pain Scale, the validation study of which was then funded by Parkinson's UK, who requested a patient completed questionnaire (King's PD Pain Quest) to be added to the study, to empower patients to self-declare their pain. The success of the King's PD Pain Scale has led it to be recognised worldwide and be validated as a clinical tool capable of being used to help PD patients and clinicians in managing pain in PD. KRC, Professor K Ray Chaudhuri; PD, Parkinson's disease; CRISP, Community for Research Involvement and Support for People with Parkinson's.

"... there are academics who devote their whole career to understanding a small part of the puzzle, [...] e.g. Parkinson's. If I can be part of that process, then my future with [PD] looks more positive and the future of my three children without PD looks more certain..."

Suzanne Pitts (PwP, CRISP)

"... CRISP is a good representation of everyone involved in PD... it has helped us understand how research works and the steps involved. It allows for more appreciation of the work done and what needs to be done..."

Eros Bresolin (PwP, CRISP)

would like to be involved, subsequently, on accepting, they were sent a formal letter of invitation. Since this initial recruitment, leaflets and informative posters have been created and placed in clinics to help encourage patients and the public to participate in research.

This group later renamed itself as CRISP (Community for Research Involvement and Support for people with Parkinson's). Furthermore, the logo for CRISP itself was designed by one of the Patients with Parkinson's (PwP) representatives. CRISP was created to incorporate the requirements and guidance from the NIHR regarding conducting successful and meaningful research for PD patients and carers. It therefore runs in line with INVOLVE guidelines and is supported by several other research organisations including EUROPAR (European network for Parkinson's), Parkinson's UK and London South CRN (Clinical Research Network).[34] The concept behind this group is underpinned by the fact that they work to contribute towards the design and development of research projects in accordance with patient and caregiver opinions and needs.[34]

What are the aims of CRISP?

CRISP is based at King's College Hospital in South London and predominately deals with Parkinson's based research. They meet with representatives from each group working to discuss (a) the design, development and practicality of research projects, (b) discussing and reviewing current research, (c) gathering patient and public opinions on proposed projects and (d) generating novel concepts for research the group feels needs to be undertaken.[34] The primary aims of CRISP can be summarised into two categories; research initiatives and raising research awareness. See Figure 2 for a diagrammatic representation of CRISP aims, with a few examples.

CRISP & Research

The members of CRISP typically meet on a quarterly basis with each meeting lasting around two hours. During a meeting, researchers provide a printed list of all ongoing and proposed projects at the Trust sites. Each project synopsis is provided and discussed with the CRISP members, enabling an atmosphere whereby both researchers and members can ask questions. This form of discussion has proven to be very useful in the past. For example, one project requiring patients to attend clinic in 'off' state would need to consider how difficult it would be for a patient to arrive to the clinic in that state, hence suggestions of staying overnight at the hospital or local hotel would be more practical and achievable. With some urgent progress on new and upcoming projects arising throughout the year, the members are all reachable via email or post if their involvement is particularly useful and required prior to an upcoming meeting.

Research groups in Parkinson's, such as EUROPAR, have utilised CRISP by involving the members to participate and review new editions of patient-friendly books (i.e. the 'Fast Facts in PD: 4th edition') and helped the fine-

tuning of inclusion criteria for some research projects (i.e. PD simvastatin clinical trial) prior to submission for approval.[35] This type of collaborative work has led to many successful identifications and changes in the NHS and work worldwide, with regards to the way we approach Parkinson's patient care. One success story of a CRISP-led project has been the development of the King's Parkinson's disease Pain Scale (King's PD Pain Scale), which is now a validated scale.[36] See Figure 3 for the outline of how CRISP was involved in the making of this scale.

> *...modern treatments for Parkinson's only became available after research and testing on [PD] patients. Seems only fair, therefore, that I make my own contribution... you never know, research may lead to treatment beneficial to me...*
>
> *David Charlton (PwP, CRISP)*

CRISP & Patient awareness video

It is essential to appreciate the difference between involvement and participation, whereby patient involvement is achieved through PwP represented in CRISP, whilst patient participation is the active partaking in clinical research. CRISP works to promote both aspects through various means (i.e. leaflets, videos).

For research to be beneficial in the real world for patients, it must be trialled and tested to ensure it works. However, due to lack of public awareness and misunderstanding as to what might be expected from the patient, many researchers have patient recruitment problems.[37] This has been addressed by CRISP through the development of a video whereby CRISP members speak about their experience with active and advisory PPI. This video has now become a regular feature on the NIHR TV (https://www.youtube.com/watch?v=jERbtx-ASRAI), as well as being displayed in the clinical waiting rooms for patients. Along with the video, there has been a range of positive material such as flyers and letters by CRISP to raise awareness for research in the public.

By creating these promotional materials, CRISP has worked to help achieve goals set by research organisations. The NIHR and INVOLVE, both work to promote a multi-disciplinary approach to research whereby clinicians, researchers and senior academics should have PPI implemented in every step of the project. CRISP, since 2011, has established an essential role in fulfilling NIHR, and further the HRA, expectations of an Excellent Research Centre. This has been achieved through the identification of problems that Parkinson's patients experience and allow research to be tailored to ensure the actual problems are being addressed.

Future of PPI

Depending on the funder, PPI is becoming a mandatory condition on many applications for researchers. Furthermore, dedicated toolkits and frameworks are now set-up (i.e. Public Involvement Impact Assessment Framework (PiiAF) to aid in assessing PPI impact on projects. However, some funding bodies still do not set PPI as a mandatory requirement, moreover funding for PPI is currently limited. Movement disorder specific PPI are still sparse, and following the success and achievements of CRISP, it is necessary to establish specific PPI in each research centre in the UK. This will address the need to improve patient and public knowledge about research participation and involvement.

ACKNOWLEDGEMENTS

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Challenges and opportunities for UK independent providers of neurorehabilitation services navigating the current UK NHS Commissioning Environment

By Chloë Hayward

Brain injury is the leading cause of death and disability worldwide; approximately one million people live with an Acquired Brain Injury in the UK. Specialist neurorehabilitation (NR) services play a vital role in the management of patients admitted to hospital by taking them after their immediate medical and surgical needs have been met, maximising their recovery and supporting safe transition back to the community. The extent of the NR programme delivered varies enormously due to the complexity of the brain and the nature and severity of the injury. This diversity makes NR planning and service provision challenging and complex.

The Department of Health Specialist Services National Definition Set (SSNDS) 3rd edition published in 2009, defined four categories of patient need (A,B,C,D) ranging from complex or profound disability (Category A), to patients with a wide range of conditions but who are usually medically stable (Category D). SSNDS also defines three levels of specialist service (1, 2 and 3); Level 1 Units are high cost/low volume services for Category A patients, Level 2 Units mainly provide services for Category B patients and Level 3 Units mainly serve Category C and D patients. This provides a framework for the planning and commissioning of specialist NR services.

Since the reorganisation of the National Health Service (NHS) following the Health and Social Care Act 2012, tertiary specialist NR for Category A patients are commissioned directly by NHS England. Local specialist and general services are commissioned by the Clinical Commissioning Groups (CCGs).

The UK specialist Rehabilitation Outcomes Collaborative (UKROC) database is a national dataset for specialist NR services. UKROC collates case episodes for inpatient rehabilitation from all specialist NR services across the UK and provides the commissioning dataset for specialist NR services and national benchmarking.

UK Independent Service Providers (ISPs) must navigate this complex NHS commissioning environment to ensure NR beds are utilised and funded 24/7; this presents many challenges and few opportunities.

Knowledge base

ISPs provide more NR beds than the NHS and they should be recognised as providers not 'add-ons'. Often the commissioning of NR services falls under the banner of 'long-term conditions'. NR is a complex process of assessment, treatment and management by which the individual, and their family/carers, are supported to achieve their maximum potential for physical, cognitive, psychological and social participation in society and quality of living. Commissioners need a basic understanding of the complexities involved in the assessment, management and delivery of outcomes for individuals with brain injury.

Specialist rehabilitation or nursing care?

There are standards and guidelines for ISPs; they have to demonstrate that they can assess the complexity of NR needs, provide a level of NR interventions and have the facilities to achieve this. ISPs must evidence measurable outcomes that demonstrate a useful gain. To be eligible for Levels 1 and 2, ISPs must register with UKROC and submit a dataset for each case episode. This is challenging for those ISPs who predominantly provide neurobehavioural rehabilitation where the outcome measures do not comply with UKROC requirements.

NR care plans are designed and implemented by interdisciplinary teams who have undergone recognised specialist NR training. By law, NR providers must register with the Care Quality Commission, however, the requirements are minimal and many care homes claim to provide a NR service when they lack the necessary experienced interdisciplinary team.

Patient referral process

The patient referral process can be complex, challenging and extremely time-consuming. Currently beds are 'under-commissioned', despite the waiting lists of patients requiring NR. In order to 'attract' referrals ISPs have to maintain and grow their reputations, demonstrate robust outcomes, facilitate networking with CCGs and market their services comprehensively in the catchment area. Patients are referred via several routes; depending on the funding stream e.g. NHS Hospital Trusts, NHS Continuing Care and medico-legal. The challenge of 'filling beds' depends on assessing patients, developing NR programmes and then confirming funding. Many ISPs also have to make arrangements for where the patient will go post-discharge, before they can be accepted.

Cost-efficient service provision

Convincing commissioners about the cost of NR has always been a challenge. There is now a substantial body of trial-based evidence and other research to support both the effectiveness and cost-effectiveness of specialist NR which needs to be constantly communicated.[1] The cost of providing early specialist NR for patients with complex needs is rapidly offset by longer-term savings in the cost of community care, making this a highly cost-efficient intervention.[1]

UKROC recently reported data on functional outcomes, care needs and the cost-efficiency of specialist NR for a multicentre cohort of 5739 inpatents with complex neurological disability, and compared different diagnostic groups across three levels of dependency.[2] Outcome measures were recorded on admission and discharge and all received specialist inpatient multidisciplinary rehabilitation. All groups showed significant reduction in dependency between admission and discharge on all measures. There was also a mean reduction in 'weekly care costs' and the time taken to offset the cost of NR was 14 months in the high dependency group.

The current national bed tariffs are flexible and provide ISPs with the opportunity for local negotiation.

Staff recruitment and retention

Specialist rehabilitation requires input from a wide range of NR disciplines e.g. rehabilitation-trained nurses, physiotherapy, occupational therapy, speech and language therapy, psychology, dietetics, orthotics, social work, as well as input from consultants trained in rehabilitation medicine and other relevant specialties e.g. neuropsychiatry. Having the appropriately skilled staff in sufficient numbers to provide rehabilitation at a level of intensity commensurate with the patient's needs is on ongoing challenge. There is often a shortage of qualified staff e.g. rehabilitation-trained nurses. However, ISPs do have the opportunity to provide salaries/benefits that are not governed by the NHS.

Independent Neurorehabilitation Providers Alliance (INPA)

The Independent Neurorehabilitation Providers Alliance (INPA) was established in 2012 with the key objective of improving standards in the independent sector.
For further information, please contact:
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Neuro-palliative care – a growing need

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'Palliative Care (PC) is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual' [1]

What is PC?

Developed at St Christopher's Hospice, London in the 1960s, palliative care was aimed at achieving relief for pain in the context of advanced cancer. There has been increasing recognition of the needs of patients with advanced and complex symptoms with non-malignant conditions.[2] The modern aims of palliative management are to provide the best quality of life possible, providing integrated care, supporting patients and families with emphasis on communication and planning. All should be tailored to individuals; throughout the course of disease.[3]

PC in neurology-is it needed and who should supply it?

Patients with neurological disorders have a high symptom-burden with uncertain trajectories and often a protracted course, dealing with significant disability for a long period of time.[4] Furthermore, managing progressive non-malignant conditions has an added element of complexity. Unlike many cancers which have relatively predictable trajectories and a morbidity limited to the last five months of life; non-malignant conditions such as atypical Parkinsonism can have pronounced, early disability which the patient lives with over years. This is coupled with the uncertainty of these conditions.

There is a distinction between general palliative care which can be provided by all clinicians and medical teams and Specialist Palliative Care (SPC). SPC is provided by specialist nurses and doctors frequently based in a hospice setting and their caseloads are defined by complexity. For example, not all patients with cancer will be seen by an SPC doctor[5] (see Figure 1).

The palliative approach infuses patient care from diagnosis with recognition of both the individual needs of the patient and family, addressing not only physical but emotional, social and spiritual needs[6] and can be thought of as general PC. The palliative approach has for some years been the cornerstone of Motor Neurone Disease (MND) practice. Borasio[2] describes palliative care in MND as the paradigm which other neurodegenerative diseases should consider when trying to establish good holistic management. Essentially, all clinicians and medical teams can supply good, basic palliative care. Part of the palliative approach is recognising when the patient may require more specialist input from SPC.

What are the challenges in neurological PC?

Recent work has shown PC requirement and symptom-burden of non-malignant disease can be as prevalent as advanced cancer. Renal failure, COPD and advanced Parkinsonism are associated with symptoms often treated effectively by PC for malignancy, for example pain and nausea.[9,10] See Table 1 for specific challenges in neurological disease.

Progressive, non-malignant disease often has a background of decline with unpredictable crises; which may result in good recovery, decline but survival or death.[3]

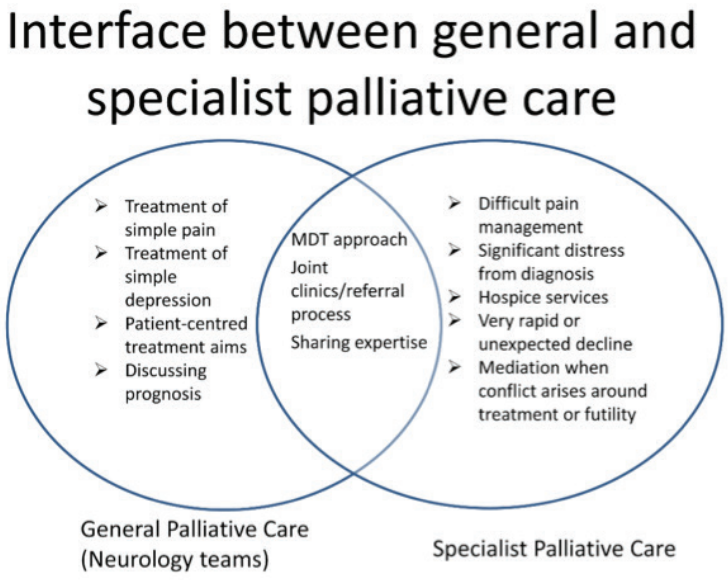

Figure 1: The overlap between general and specialist palliative care. Adapted from 6-7 Taken from Wiblin.[8]

Table 1: Specific challenges and approaches in neurodegenerative disease		
Condition	**Challenges**	**Management**
Cerebral Malignancy	Seizures	Education to carers
		Non-oral treatment for generalised convulsion e.g. buccal midazolam and ability to use it (especially if being nursed at home)
		Regular oral anticonvulsant if recurrent
		Advanced plan to convert to syringe-driver delivered benzodiazepine at end-of-life
Creutzfeldt-Jakob Disease	Myoclonus	Benzodiazepines (oral or subcutaneous)
	Rapid cognitive decline	Carer support and hospice input
	Agitation and Distress	Reassurance and nursing experience in neurological/palliative care setting, benzodiazepines, antipsychotics
	Bulbar problems	Open MDT discussion involving family of suitability of NG/PEG feeding (will depend upon disease trajectory and tempo)
Motor Neurone Disease	Depression	May also be apathy or pseudo-bulbar affect affecting mood and motivation. SSRI and education of carers (especially in apathy)
	NIV or invasive ventilation	Monitor for nocturnal hypoventilation; consider NIV if present. Implications of invasive ventilation should be clearly discussed with patients and families and not undertaken lightly and full MDT input and review required
Huntington's disease (HD)	Chorea	Tetrabenazine (can worsen depression)
	Heritability	Trained genetic counselling and support for family and patient
	Suicide	After pneumonia, second most common cause in death in HD; psychological support, treatment of depression, monitor for suicidality. Family support

It is often difficult for clinicians to predict the terminal phase, making planning (for example trying to ensure the patient spends the last days of life in their preferred setting) challenging.

This uncertainty can be difficult for patients and relatives but a good relationship with a clinician can help, providing communication tailored to the patient's needs and wishes.[11] Information should never be imposed on a patient not ready or able to hear it.

One of the key pillars in a good palliative approach is advanced planning and statement of preferences. But PC is not and should not be a tick-box exercise; completing a form is not the ultimate aim. Not all patients will feel able to take part in these discussions. It may take time and accumulation of trust to allow the person to consider their future. Some may never do so. This is not a failure and it may be that even signposting future decline is enough for patients and families to make their own adjustments and begin acceptance.

I have learned that dividends can be made from development of good relationship with a healthcare professional over years of illness, incorporating open communication, multidisciplinary care and holistic symptom-control. The neurologist, as the main contact for patients with neurodegenerative disease and specialist knowledge of the disease process is key in providing this.

The future of neurological PC

Don't we all provide palliative care anyway? Whether a condition has disease-modifying treatments available (such as in relapsing remitting MS), is relentlessly progressive (MND) or has a long, chronic course with significant physical symptoms (Parkinson's disease), the same principles apply to improve quality-of-life. Most clinicians have an appreciation for this; a survey of neurologists found that limited time and a lack of training posed barriers to palliative management but the need was recognised.[12] Many of us do provide good care with a holistic approach. As we refine our services and design models of care for the future, an awareness of how patients' needs can be served and how we provide them in collaboration with SPC colleagues is required, locally and nationally.

People are living longer with ever-increasing disease burdens and co-morbidity, so the need for palliative care will grow. It is unrealistic that SPC can absorb all of these patients. One solution might be more GPs and specialist consultants developing subspecialist interests in palliative care in particular areas, ensuring better experiences for patients and families, referring only the more complex cases on to SPC. Training, multi-disciplinary support and time to deliver these services should be a priority in the future.

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Measuring neurobehavioural disability using the SASNOS: applications and new developments

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Neurobehavioural disability (NBD) resulting from acquired brain injury (ABI) potentially has significant consequences, including challenging behaviour which is a greater long-term impediment to community reintegration than physical disability.[1] Consequently, availability of reliable, valid means of assessing NBD is highly desirable. Standardised measures have known psychometric properties that inform validity and reliability. However, a review of well-known NBD measures revealed that many were lacking these properties, rendering measurement problematic.[2]

The 'St Andrew's – Swansea Neurobehavioural Outcome Scale' (SASNOS) was developed to fill this gap.[3] Forty nine items capture five major domains of NBD, each of which has two to three subdomains. Items comprise a statement regarding a symptom of NBD, rated using a seven-point scale. Assessment follows observation of a person over a two week period.

A major strength of SASNOS is availability of data from neurologically healthy people, facilitating identification of NBD symptoms in individuals with ABI more prevalent than amongst the general population. Ratings are transformed to standard scores with a mean of 50 and standard deviation of 10; higher scores reflect less NBD symptoms. SASNOS has robust psychometric properties, meaning single assessments of NBD produce dependable results.

Since 2011 SASNOS has seen international use, including Australia, Canada, Demark, Spain, The Netherlands, Ireland and New Zealand. Within the UK, it has been endorsed by organisations providing neurorehabilitation and it is routinely used to monitor clinical and cost-effectiveness of services.

Developing the instrument has forged strong partnerships between Swansea University and health providers, most significantly Partnerships in Care, which has a growing network of neurobehavioural rehabilitation services, the most recent of which is Manor Hall near Stirling. Currently, there is little specialist provision of this type in Scotland so the imminent launch of this new service is welcome news.

An early account of SASNOS was described previously in ACNR.[4] Collaboration between Swansea University and Partnerships in Care continues to foster research to improve the instrument for the benefit of patients. Three innovative developments will be briefly described.

First, context is critical to the meaningful interpretation and application of SASNOS scores. Ratings made concerning patients in residential rehabilitation programmes will reflect prevalence of behaviours and functional abilities in the context of rehabilitation; it cannot be assumed that results obtained will have universal validity and be generalisable to other settings (e.g., home, community). Sometimes ratings are comparable with neurologically healthy people and can provoke discharge to a less restrictive placement. However, whilst rehabilitation ideally results in long-lasting change, some improvements require ongoing support which standardised assessment scores in the 'normal' range do not indicate by themselves. This increases the risk of some people being discharged without the support needed to maintain autonomy.

In response to this, we propose that supplementary dependency ratings are completed for each SASNOS item (under review).[5] Dependency ratings calibrate standard scores to estimate the effect on ratings without support. If the person is truly autonomous, standard and weighted SASNOS scores are identical. However, where provision of support underpins absence of NBD symptoms, there is clear dissociation between scores (see Figure 1). In their paper, the authors articulate reasons for making supplementary dependency ratings, describe profile types emerging from these, present an illustrative case example, and report the results of a user survey testifying to the validity and clinical usefulness of the new development.

The second innovation concerns responsiveness, the ability to measure meaningful change over time (under review).[6] A major use of SASNOS is in repeated assessment, including tracking response to rehabilitation. However, in practice, determining when a score-difference on a standardised instrument indicates real change is difficult. Indeed, whilst many instruments have evidence confirming validity and reliability, information on responsiveness is less apparent. Some have none, or use aggregate data and tests of statistical significance, which do not translate obviously in interpreting difference scores for individual patients. There is also no agreement on one 'gold standard' method for determining responsiveness. The authors examine this issue in relation to the SASNOS, exploring multiple methods to determine responsiveness and present several indices to fit a range

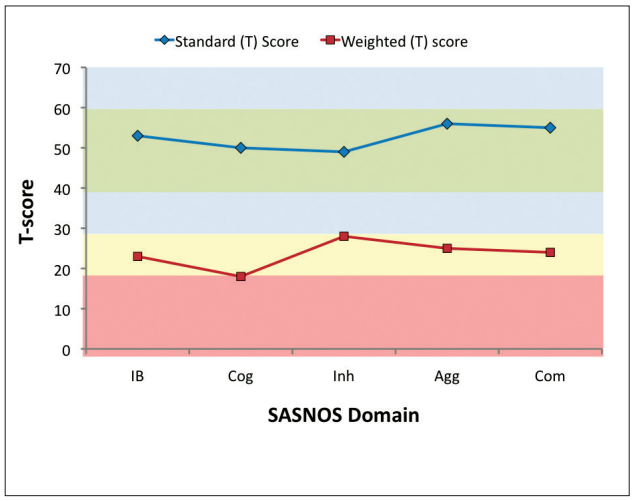

Figure 1: Comparison of standard and weighted SASNOS domain scores; whilst standard scores all fall in the expected range for neurologically healthy controls, weighted scores suggest absence of NBD symptoms is attributable to support received (Key to axis labels: 'IB – Interpersonal Behaviour', 'Cog – Cognition', 'Inh – Inhibition', 'Agg – Aggression', 'Com – Communication'.)

of applications. For clinical use they favour thresholds derived from the Standard Error of Measurement, which generates minimum score-difference values for SASNOS. This innovation gives clinicians confidence that higher scores on reassessment exceed variation attributable to error in the instrument and reflects 'meaningful' improvement for patients.

The final innovation is a revised SASNOS. All standardised assessments can be improved and should be continually reappraised and modified. Whilst feedback since 2011 has been extremely positive, the scope and number of items in the 'communication' domain can nevertheless be improved. Consequently, 30 new 'communication' items have been constructed and a study implemented to populate content of SASNOS-Revised (SASNOS-R). Whilst SASNOS was standardised using ratings from a sample of 100 neurologically healthy people, the current study will re-examine all the items by recruiting a much larger sample from the general population as well as collecting multiple ratings over time. Readers wishing to contribute to this important work can participate here: http://bit.ly/SASNOSsurvey. A further study will also collate SASNOS-R ratings from a larger sample of people with acquired and progressive neurological conditions than originally employed to fully determine the tools clinical utility.

For those interested in learning more about SASNOS, the authors will be speaking alongside other leading experts at a major conference regarding NBD entitled 'Reducing the burden of neurobehavioural disability after acquired brain injury: past present and future', being held in Swansea on 28th November 2016 – see http://bit.ly/TicketsABISwan16

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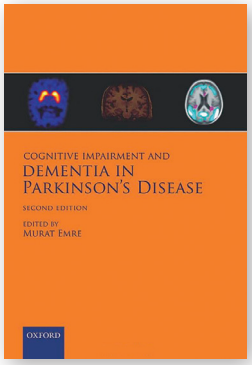
Cognitive Impairment and Dementia in Parkinson's Disease – 2nd Edition



Editor: M Emre (ed.).
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Price: £75
Pages: 313

Reviewed by: AJ Larner, Cognitive Function Clinic, The Walton Centre, Liverpool.

Of the non-motor features of Parkinson's disease (PD) which have attracted increasing awareness in recent times, cognitive impairment has certainly been a significant focus of attention. For example, since the appearance of the first edition of this well-received text, originally published in 2010, new diagnostic criteria for mild cognitive impairment (MCI) in PD have been published (Mov Disord 2012;27:345-56).

Older readers may recall an occasional but recurrent feature in the BMJ of the late 1980s entitled "What's new in the new editions?" written by the late Clifford Hawkins. Following this precept, this new edition contains two new chapters, one of which (17) specifically addresses PD-MCI, giving a cautious welcome to the aforementioned criteria but emphasising the heterogeneity of this construct which does not define a discrete entity either clinically or pathophysiologically. Definition of PD-MCI subtypes will be necessary to derive any prognostic significance from this diagnostic label. The other new chapter (11) is also related to this issue, addressing the topical matter of disease biomarkers. A number of such CSF, genetic and neuroimaging biomarkers have been suggested, but "although several promising markers have been identified, findings have not been replicated or are inconsistent for the vast majority of candidates" (p. 145). Hence PD lags Alzheimer's disease in this respect, a point also emphasised in the final chapter (22) which aims to give some predictions for the future: "we are more than a decade away from mechanistic therapies" (p. 303) seems pretty secure.

As in the previous edition, other chapters cover the clinical, neuropsychological, neuropsychiatric, neuroimaging, neurophysiological, neurogenetic, neurochemical and neuropathological basis of cognitive impairment in PD, as well as treatment options (still limited to cholinesterase inhibitors). I found the chapter on the interrelationships of gait and cognition in PD particularly informative. As for the cognitive heterogeneity, Kehagia's "dual syndrome" hypothesis (dopaminergic/fronto-striatal and cholinergic/visuospatial-attentional impairments) may go some way to explain these features.

There is only brief discussion (20) of cognitive screening instruments that may be used to detect cognitive impairment in PD (e.g. MMP, PANDA). More pragmatic content on the pros and cons of these might have been desirable, likewise in terms of their evaluation. Bronnick's chapter on cognitive profiles (4), the first edition of which was a significant stimulus for me to think more about effect sizes as a way to evaluate cognitive instruments, sadly confused me in this edition, specifically on visual memory performance in PD-D and DLB (not clear which is worse, as there are seemingly mixed messages on p. 38 and Table 4.4 p. 39). Other (minor) gripes relate to the smaller font size compared to the first edition (a challenge for the progressively presbyopic), and references which go awry (compare text and bibliography in chapters 2 and 7).

Of course, for new readers the new edition stands on its own merits and it is clear that this volume contains much valuable information on cognitive impairment in PD and can be thoroughly recommended for all those involved with the assessment and management of these problems.

Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease – 5th Edition

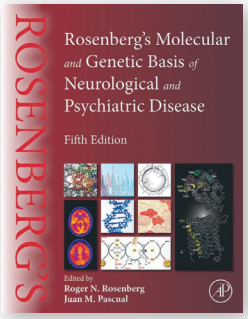
This book is 1464 pages long, and available both in print and electronic formats. It is priced at $155 (good value per page) and the print and electronic formats together are offered at a concessionary rate ($186).

Deferentially known as the 'Bible of Neurogenetics', it was first published in 1993. This 5th edition has more than 100 chapters and double that number of contributors. All of the chapters have been meticulously updated by previous contributors and 'new blood' authors of international pedigree. The book covers a wide range of neurological and psychiatric disorders; new chapters in the current edition are those on the ethics of cognitive enhancement and mental impairment.

We all understand that life starts at microscopic level and that genetic codes are reflected in all biological microstructures. We are also aware that illness correlates with Genetics. Better understanding at the genetic level will guide us on the path of correctly investigating, diagnosing and treating illnesses. Such understanding is the aim of this volume as a whole, perhaps best encapsulated in the chapter on Gene Mapping.

In its mechanics, the book is well indexed and the text is complemented by tables, diagrams, statistical data, photographs and radiographs. Research articles and relevant websites are also cited. Furthermore, the work is printed in colours which are both attractive to the eye and helpful for clarity.

The textbook caters for a wide readership from students and researchers in the neurosciences, in Psychology and in Genetics, to practitioners, including doctors and genetic counsellors. Genetics is a rich furrow ploughed by the setters of examination questions and, while a book of this weight is hardly suitable as an exam crammer either for undergraduates or higher level trainees, it offers a wealth of insight and a depth of understanding to those wishing to consolidate their exam preparation.



Edited by: Roger N Rosenberg and Juan M Pascual
ISBN: 978-0124105294
Published by: Academic Press.
Price: £155

Reviewed by: Dr Lakshmi Kottidi Navakoti MD, MRCPsych, ST4 in Old Age Psychiatry, Mersey Deanery, UK.

As a career psychogeriatrician, the chapters most appealing to me were those on Alzheimer's, Parkinson's, bipolar disorder, depression and schizophrenia. The book has helped to provide explanations on the genetic basis of these illnesses to my patients, and their families. In particular, I was surprised by the chapter on Pain Genetics. Pain is not to be regarded as a psychiatric disorder but has a strong correlation with mental illnesses. In my day-to-day practice, I come across a large number of my patients with anxiety, depression, schizophrenia or dementia suffering from deterioration in their mental state because of comorbid pain conditions. They are often referred to 'medical' clinics of one sort or another. Conversely, huge numbers of patients with chronic pain conditions, poorly responsive to medical interventions are referred to us in Psychiatry, to rule out psychological contributors. Some insight into the Genetics underpinning this complex clinical situation was very welcome.

All clinicians will have their own home 'territory' among the chapters. Psychiatrist colleagues of mine specialising in Learning disability will turn to the chapters on Down syndrome, Rett syndrome and autistic spectrum disorder. Neurologists will pore over the chapters on dystrophies of one sort or another, epilepsy, stroke disease, Huntington's and many others. But the clinical manifestations of genes acting on the nervous system really know no bounds and internists may also consult the chapters on metabolic disease and others.

Overall, I felt that the book was good value for money, by weight but also by content. It is a 'must have' for medical libraries.

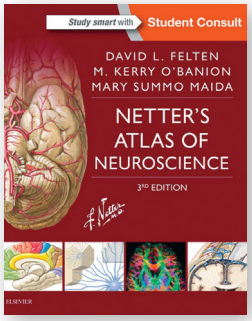
Netter's Atlas of Neuroscience – 3rd Edition

The aim of this book is to teach medical students, and others pursuing any subject with a basis in Neuroscience, the principles of Neuroanatomy, together with histology and neurophysiology. It also deals with the essentials of developmental neuroscience. In brief, the book aims to give the reader an understanding of the nervous system. As an atlas, its emphasis is on visualising the macro- and microstructure as well as depicting the topographic and systematic organisation of the nervous system, integrating all these to provide the 'big picture'.

Its success depends on Netter's distinctive drawings, their anatomical detail and their capacity to show interrelations between the various systems, reinforced by complementary clinical insights presented as 'boxes'. This approach resonates with students in the early years of their medical lives and with trained clinicians alike.

The atlas is divided into three sections: Overview of the Nervous System, Regional Neuroscience and Systematic Neuroscience, each further subdivided.

Firstly, Section One illustrates basic principles and focuses on Neurons and their Properties, followed by a further subsection, Skull and Meninges. Three additional subsections deal with the Brain, Brain Stem and Cerebellum and the Spinal Cord. The Ventricles and the Cerebrospinal Fluid, as well as the Vasculature are covered in subsections six and seven. The end of section one is devoted to Developmental Neuroscience. After an overview, the second part deals with Regional Neuroscience, taking a much more detailed look at different parts of the Peripheral Nervous System and the central nervous system, presented in sequence – Spinal Cord, Brain Stem and Cerebellum, Diencephalon and Telencephalon. In contrast to the topographic order of Section Two, the third and last section focuses on Systematic Neuroscience, exploring in detail the functional anatomy of Sensory Systems, Motor Systems and Autonomic-Hypothalamic-Limbic Systems.



Authors: David L. Felten, M. Kerry O'Banion, Mary E Maida.
Published by: Elsevier, 2016.
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Price: £40.99
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Reviewed by: Christian Komandzik, Medical Student, University of Regensburg, Germany.

When it comes to graphical material, readers will see the full colour palette in the classical drawings by Frank Netter and those by John Craig and Carlos Machado, both of the Netter 'School', as well the as animated illustrations of James Perkins. There are further illustrations showing different neurological imaging methods, photos of histological material, tables, and schematic diagrams.

Apart from the hard copy, the atlas also serves as an eBook accessible on IOS and Android devices, or on the web. These formats display the whole book and give additional options, so that users can enlarge images, make notes or test themselves in labelling the anatomic illustrations. Furthermore, students may watch 14 short videos presenting applied neuroimaging methods such as MR-Imaging, Diffusions-Tensor-Imaging, Angiographies or 3D-images of the brain. The visual quality of these videos is low, but they are helpful in bridging the divide between theory and clinic.

In terms of the volume's limitations, readers should not expect detailed examination of the bones, ligaments or muscles of the cranium or cervical spine. The integrated eBook offers a small number of educational features, but users should not expect too much...When it comes to conceptual neuroscience on a microscopic and molecular level, the atlas contains far less than the typical textbook.

At its best, Netter's atlas will provide good value-for-money as means of operating the visual channel of learning to complement a more conventional text.

Alzheimer Association International Conference

Conference details: 24-28 July Toronto, Canada. ***Report by:*** Daniel Blackburn, Consultant Neurologist and Honorary Senior Lecturer, Sheffield Teaching Hospitals NHS Trust and Simon Bell, ARUK Clinical Fellow and Neurology Speciality Trainee, Sheffield Teaching Hospital NHS Trust & University of Sheffield. ***Conflict of interest statement:*** The author declares that there are no conflicts of interest.

Venue

This year the AAIC was held in Toronto Canada. This city of 2.6 million people has a very welcoming feel. The weather in July is amazing, and there are plenty of things to see and do. Highlights include the CN Tower, Niagara Falls, a baseball game at Rogers Stadium, and a visit to Kensington Market.

The conference center itself is a huge building that straddles Union station in the middle of Toronto's financial district. The conference rooms had good visibility, but maybe were set at a temperature a little low for those of us not accustomed to North American air conditioning. Snacks and coffee were available throughout the day, but lunch was not provided. This in one sense was a positive though as it gave the delegates the chance to enjoy the great food on offer in Toronto served at establishments such as Ravi's Soups.

CN tower lit up in the colours of the AAIC

The welcome reception

Dan presenting his paper

The conference

The plenary speakers gave a steer on the direction for Alzheimer's Disease (AD) research. In summary there is a move for a broader view of AD, away from the narrow amyloid and tau disease construct. This move is ultimately driven by failure of new medications and with other targets needing to be assessed.

Gabrielle Constatin (Italy) reviewed many years of study on peripheral inflammation. She highlighted neutrophil cycling across blood vessels, attracted by amyloid plaques and the potential avenue of blocking translocation by drugs used to treat Multiple Sclerosis (MS). The systemic immune theme was also covered by John Hardy (UK). Genome Wide Association Studies (GWAS) hits from AD patients are involved in two main pathways; inflammation and lipid metabolism. Prof Hardy suggested that AD has a component mediated by innate immunity and that future research should focus, in part, on the systemic immune system. Prof Hardy divulged his thoughts on the selective vulnerability of cell types in various neurodegenerative diseases; AD-pyramidal cells fail due to vulnerability to proteasome pathways whilst Parkinson's Disease (PD) neurons have vulnerability due to weaknesses in the mitochondrial complex 1; The other GWAS hits for risk factors for AD (including CLU, PICALM and CR1) do not approach APOE4 which has an odds risk of 4 compared to others with an odds risk of <1.5. APOE and selective vulnerability was also covered in the session by Jane Driver who switched careers from oncology to AD, motivated by the lack of therapies for AD. In the field of Oncology >200 cancers related drugs have been approved in the last 20 years. She highlighted the fact that the longevity of neurons, allowing them to survive for 80 plus years, is accomplished by passing critical metabolic functions to glial cells. The tradeoff of this relationship is the vulnerability to death. This is in contrast to peripheral cycling immune cells that replicate quickly and have an increased risk of cancer. This analogy becomes important when we consider the PIN1 gene which helps maintain telomeres in white cells but acts on Amyloid Precursor Protein (APP) in neurons. Thus there might be an inverse link between cancer and AD. There is data that suggests an inverse relationship between malignancy and AD, but clearly this is subject to many biases. Professor Driver suggested that early onset AD (genetic, rapid progression) is very different to Late Onset AD (metabolic disease, slower progression). She summarised her comparison with a call for the investigation of multiple targets in AD, such as is seen in oncology therapies. In particular targeting metabolic health with exercise, mitochondrial support, insulin signaling, and metformin action on mitochondrial complex one activity.

Another plenary speaker, Laura Baker (USA) discussed how exercise might help to treat Mild Cognitive Impairment (MCI) and AD. This study selected sedentary patients with MCI. Dr Baker suggested that studies involving exercise need to last at least 6 months because the main effect, as shown on functional MRI, is on frontal network connections. She suggested longer studies are required to see if there is a long-term effect on improving or maintaining memory. As exercise may not be amenable to all patients other targets for a metabolic pathway intervention were mentioned as another way to exploit this type of intervention. Dr Suzanne Craft discussed the ketogenic diet as a treatment not just of epilepsy but also for AD. Dr Samuel Henderson presented further work from a company, Accera, which is running a phase three study of AC1202, a medium chain fatty acid that produces ketones/ketosis. There were two sessions on mitochondrial function in AD. Dr Eugenia Triushina from the Mayo clinic Rochester presented data on CP2, a complex 1 partial antagonist that is effective in cell based assays and animal models (3Tg models) of disease. This compound restores mitochondrial transport, protects against Reactive Oxygen Species (ROS) and against Abeta and tau toxicity. Metformin, another drug that inhibits complex 1, has been reported in data from United Kingdom–based General Practice Research Database (GPRD) to increase the risk of developing AD (an effect not seen with sulfonylureas). Thus the role of complex

one and drug action on it requires considerably more work.

There was not much out of therapeutic trials. There remained a lot of papers on amyloid and tau PET studies but this field does not appear to be moving fast. There is increasing interest in the vascular contribution to Alzheimer's disease and separation in clinical diagnosis is reducing. There was a debate as to whether white matter hyperintensities (WMH) should be part of the diagnostic criteria for AD, with some data from the Dominantly Inherited AD (DIAN) cohort.

On the clinical front there was an interesting paper which used laser-capture microdissected plaques from the hippocampus of rapidly progressive AD (rpAD) patients. rpAD is associated with having 14,3,3, in CSF and lower frequency of APOE4. Eleanor Drummond (NYU, Case Western) presented the data from 22 rpAD and 22 sporadic normal progressing cases. The rpAD cases had no mutations in genes known to cause fAD (PSEN or APP) nor in prion genes. Proteomic analysis using mass spectrometry found decreased protein expression including GFAP, gelsolin and abeta. There were less astrocytic proteins and more neuronal proteins, including vesicular proteins and actin cytoskeletal proteins. They found one protein 11 fold higher in the sporadic group but they had not identified or were not able to provide more information on this protein.

Finally the Canadian health system is under the same amount of pressure as the NHS. Waiting times to be seen in memory clinics are very long, up to 6 months. A series of talks on models to improve care and management of people with dementia in Ontario, Quebec and Saskatchewan were presented. Dr Linda Lee, has a long history in this area, developing the Primary Care Collaborative Clinics since 2006. This is a single point of access, integrated and collaborative, interdisciplinary clinic that included nurse practitioners, social workers and pharmacists. There is a 5-day training programme for the clinic for all personnel. This includes 2 days of workshops and mentoring. There are booster days to maintain skills. A population of over 1.7 million is covered by 170 primary care practices in Ontario. 90% of referrals were managed in primary care. The 10% referred on for secondary care assessment included complex co-morbidities, atypical presentation, FTD, DLB and rapid progression. Geriatrician chart audit had revealed high levels of agreement on diagnoses. In the UK, secondary care memory clinics are diagnostic rather than management led and more primary care diagnosis would be likely to be cost effective, but assessing accuracy of diagnoses would be important.

A final interesting point from the original amyloid immunisation study was presented by James Nicoll (Southampton, UK). Neuropathological follow-up of cases from the original immunisation trial (AN1792), confirmed AD in 16 out of 21 of the participants; leaving 5 without AD (1=PSP, 1=DLB, 1= VaD and 2- FTD-TDP43). This highlights the importance of neuropathological follow-up in clinical trials in AD. Of the 21 participants 18 received the active drug and 3 placebo. Professor Nicoll showed long term amyloid plaque removal in those who received immunisation, although these results are impaired by the fact that only 1 out of the 3 participants who received placebo had AD.

Overall the conference was in a great location, with excellent amenities. Topics covered in the conference were in general very interesting, and able to highlight important areas of future research and areas that need further development. Next year's conference comes to London in the UK, hopefully the AAIC organisers will take a leaf out of the 2012 Olympics committees book and provide an excellent conference.

Obstetric Neurology

Conference details: 8 June 2016, W12 Conferences, Hammersmith Hospital, London UK.
Report by: Dr Ang Dawson, Clinical Research Associate, Institute of Neurology, University College London/University College London Hospital NHSFT UK. ***Conflict of interest statement:*** The author declares that there are no conflicts of interest.

Imagine you are urgently called to a 31-year-old female patient in A+E. She has suffered a tonic-clonic seizure and remains unresponsive, dyspnoeic and hypotensive with a fixed and dilated left pupil. No doubt it is with a degree of anxiety and foreboding that you hurry to see her. But now imagine she is also eighteen weeks pregnant and the situation suddenly becomes extremely worrying to the point of terrifying. From sudden onset severe headache to progressive limb tingling, neurological symptoms in pregnant women take on a whole new level of significance.

Obstetric Neurology is organised by Dr Pooja Dassan, Consultant Neurologist and Miss Mandish Dhanjal, Consultant Obstetrician and Gynaecologist (maternal medicine specialist) at Imperial College London NHST and is for obstetricians, neurologists and general medics involved in the care of pregnant women with neurological problems. The expanded 2016 version comprised a full day of stimulating talks and case presentations by experts in their specialist fields, providing delegates with necessary up-to-date knowledge to respond effectively and confidently to a neurological problem in pregnancy.

Delegates enthusiastically settled into the comfortable air-conditioned suite of the W12 Conferences Centre at Hammersmith Hospital, London, on a hot and humid June day. Many were from London but others from as far as Scotland, the Republic or Ireland, Portugal and even Canada. Some 38% were consultants in neurology, obstetrics and gynaecology, maternal medicine, fetal medicine and general medicine or GPs. Around 50% were ST2-ST7 training grade / equivalent doctors in these specialties.

The day began with a comprehensive overview of managing headaches in pregnancy by Dr Mark Weatherall, Consultant Neurologist, Imperial College Healthcare NHST. He outlined the different types of primary and secondary headache disorders that present in pregnancy and serious causes more likely to occur and not to be missed e.g. cerebral venous sinus thrombosis. The pros and cons of different brain imaging modalities in pregnancy were considered, but essentially where there is a strong clinical indication to scan, a scan must be done with care taken to ensure minimal radiation exposure to the fetus yet obtain the necessary information requiring a case-by-case approach with ongoing discussion between radiologist, referring clinician and patient.

Dr Robert Simister, Consultant Neurologist, University College London Hospital NHSFT, next presented a practical approach to stroke in pregnancy with a series of thought-provoking cases. There is an increased risk of stroke throughout pregnancy, particularly during the third trimester, and the same principles apply as when managing any patient with a stroke. Case reports suggest that intravenous thrombolysis is safe in pregnancy, but ideally a patient meeting the criteria would proceed directly to thrombectomy, the general direction in which stroke services are heading. Stroke risk factors must be controlled during pregnancy. For secondary prevention aspirin is a suitable antiplatelet and low molecular weight heparin safest for anticoagulation. Pregnant women presenting with stroke are typically younger: Consider rarer stroke syndromes (e.g. Moya-Moya) but remember common things are common.

After coffee, Mr David Peterson, Consultant Neurosurgeon, Imperial College Healthcare NHST described neurosurgical issues in pregnancy, for which there is no class 1 or 2 level evidence and communication with colleagues is crucial. He gave a gripping talk about his own experiences of subarachnoid haemorrhage, arteriovenous malformations (AVMs), brain tumours, disc prolapses and hydrocephalus during pregnancy, illustrated by some remarkable slides.

Dr Vinnie Sodhi, Consultant Obstetric Anaesthetist, Imperial College Healthcare NHST then described the anaesthetic challenges that can arise in the pregnant patient with neurological problems. She gave a brief tour of the different types of analgesia/anaesthesia available for pregnant women and the benefits/contraindications of each before turning to some staggering case illustrations of anaesthetic dilemmas she has experienced keeping delegates on the edges of their seats.

The first involved the 31-year old pregnant woman described at the beginning of this report. In short her problem list included: Recent severe intracranial haemorrhage (abroad) and hemicraniectomy, still awaiting cranioplasty,

underlying dural AVM, previous caesarean section, major foetal cardiac anomaly, own wish to be awake for delivery. The value of communication and teamwork (involving seven obstetric anaesthetists let alone numerous other specialists) in managing this highly complex and previously un-encountered situation cannot be overemphasised: against all odds mother and baby survived and made good recoveries.

Delegates had a chance to catch their breath and meet colleagues over lunch, before turning to the management of chronic neurological disease in pregnancy. Professor Catherine Nelson-Piercy (Obstetric medicine and Obstetrics) Guy's and St Thomas' NHSFT gave a rousing, pragmatic talk on Myasthenia Gravis, for which best practice guidelines were published in 2013. The likelihood of an exacerbation during pregnancy is 40% and 30% during the post partum period. Corticosteroids, azathioprine and ciclosporin therapy during pregnancy are safe and often essential in controlling this potentially fatal condition.

Dr Peter Brex, Consultant Neurologist, King's College Hospital NHSFT told us that consensus guidelines for multiple sclerosis (MS) and pregnancy are currently in development. Women with MS should not be discouraged from becoming pregnant; there is no increased risk of relapse during pregnancy and although a relapse is more likely within 3-4 months post partum there is no evidence of worsening long-term disability. Careful consideration needs to be given to initiating disease-modifying therapies (DMTs) in all women with MS of child-bearing age and the risks of continuing DMT treatment during pregnancy must be carefully balanced with risk of disease (e.g. currently no evidence of harm to foetus with Natalizumab).

After tea, Dr Michael Johnson, Consultant Neurologist, Imperial College Healthcare NHST reminded us of the dangers of epilepsy during pregnancy: it is the commonest non-obstetric cause of maternal death. Optimum management should begin prior to conception with counselling regarding the adverse effects of antiepileptic drugs (AEDs) on the fetus and pre-conceptual folic acid supplementation. Maternal medicine services provide an opportunity to review the diagnosis and management of seizures and there should be ongoing multidisciplinary management of fetal monitoring, pregnancy related complications, labour and delivery and the post-partum period including contraception. Poor compliance with AEDs and altered drug levels due to physiological changes during pregnancy affect seizure control. Valproate carries a 10% overall risk of birth defects and later effects in 30-40% children e.g. developmental delay, learning difficulties and should be avoided. Lamotrigine and Levetiracetam are safe: Aim to treat with one drug only at the lowest effective dose.

Finally, the course organisers closed the day with two contrasting and challenging cases, allowing the audience to test new knowledge. The first tackled the dilemma of continuing DMT in a pregnant patient with MS and delegates agreed that their approach had positively changed as a result of the afternoon's talks. The second described the management of an acute spinal cord syndrome presenting during pregnancy and reiterated the need for collaboration between all specialties involved and between experts within each separate specialty. A resounding theme throughout the day was the importance of experience, teamwork and a multidisciplinary consensus of opinion when managing pregnant women with neurological problems and no evidence-base to draw on.

Overall, the course was well-structured and delivered by superb speakers. Each talk was engaging, concise and informative but above all useful and directly applicable to clinical practise with delegates given plenty of opportunity to ask questions and make contributions from the floor. This was an excellent overview of neurological problems in pregnancy and I highly recommend it to all.

To list your event in this diary email Rachael@acnr.co.uk by 6th December, 2016

NOVEMBER

British Society of Rehabilitation Medicine Annual Meeting
Rehabilitation following major trauma
21-23 November, 2016; Manchester, UK
www.bsrm.org.uk. T. 01992 638865

Sleep Summit 2016
22-24 November, 2016; London, UK
www.sleepsummit2016.com E. sales@euroscicon.com T. 020 7183 82 31

The ILAE 2016 Concise Clinical Epilepsy Course for Junior Doctors
24 November, 2016; London, UK
See http://ilaebritish.org.uk/events/concise-clinical-epilepsy-course-junior-doctors

Reducing the Burden of Neurobehavioural Disability after Acquired Brain Injury: Past, Present and Future
28 November 2016 Swansea, UK
https://abiswan16.eventbrite.com

DECEMBER

The brain series: Memory and the brain
1 December, 2016; RSM, London, UK
Evening meeting. www.rsm.ac.uk/events/CNH02

Extending Choice in Parkinson's Disease
2 December, Park Plaza, Victoria, London, UK
Web: extendingchoice@lcwmed.co.uk E: registrations@lcwmed.co.uk T: 01444 412772

The Encephalitis Society Professional Seminar
Encephalitis: New Frontiers – Neurology & Patient Experiences
Monday, December 5, 2016; London, UK
admin@encephalitis.info T. 01653 692583.

BNPA Neurology & Psychiatry SpRs Teaching Weekend
The Essentials of Neuropsychiatry
9, 10, 11 December, 2016; Oxford, UK
T. 0560 348 3951, E. admin@bnpa.org.uk or jashmenall@yahoo.com

2017

JANUARY

15th Annual Kings Neuromuscular Disease Symposium
27 January, 2017; London, UK
http://www.kcl.ac.uk/ioppn/news/events/2017/15th-Neuromuscular-Symposium.aspx
E. samantha.smith@kcl.ac.uk

Neurology and neurosurgery - on the wards and on take
30 January; 2017; RSM, London, UK
www.rsm.ac.uk/events/CNH03

FEBRUARY

Community Brain Injury – Developing a treatment plan for cognitive, communication and emotional changes
Friday 10th February, 2017; The Oliver Zangwill Centre,
Princess of Wales Hospital, Ely, UK
Rachel Everett, E. courses@ozc.nhs.uk, T. 01353 652165

Edinburgh Stroke Winter School
20-22 February, 2017; Edinburgh, UK
http://bit.ly/1USueTl

MARCH

End of Life in Disorders of Consciousness Conference
March 24 2017; Royal Hospital for Neuro-disability
institute@rhn.org.uk www.rhn.org.uk/eol

MAY

Community Brain Injury – Developing a treatment plan for cognitive, communication and emotional changes
Friday 12 May, 2017; The Oliver Zangwill Centre, Princess of Wales Hospital, Ely, UK
Rachel Everett, E. courses@ozc.nhs.uk, T. 01353 652165

JUNE

Dizziness: A multidisciplinary approach
6-9 June, 2017; London, UK
https://queensquaredizzycourse.com/
E. thedizzinesscourse@uclh.nhs.uk T. +44 20 3456 5025

Overcoming Personality Disorders in Brain Injury Rehabilitation
Friday 16 June, 2017; The Oliver Zangwill Centre, Princess of Wales Hospital, Ely, UK
Rachel Everett, E. courses@ozc.nhs.uk, T. 01353 652165

MS Frontiers 2017
29-30 June, 2017; Edinburgh, UK
www.mssociety.org.uk/frontiers E. conferenceadmin@mssociety.org.uk

Neuroinfectious Diseases Course

Conference details: 5-6 May 2016, Liverpool Medical Institution, Liverpool, UK. ***Report by:*** Joy Ding PGY3 at The Ottawa Hospital, Ontario Canada, and edited by Dr Ava Easton (The Encephalitis Society). ***Conflict of interest statement:*** The authors declare that there are no conflicts of interest.

Have you ever been troubled by a diagnostic dilemma or a management predicament in patients with brain infections? Do you wish to learn more about possible neurologic sequelae in patients who have compromised immune systems? With the increasing use of immunosuppressant medications and global travel, neuro-infectious disease is on the rise. These infections are treatable and when missed have high mortality and morbidity.

The Liverpool Neuroinfectious Diseases Course (NeuroID) is an excellent source of learning for clinicians of all levels of training including medical students, Adult or Paediatric Neurology, Infectious Diseases, Emergency Medicine, Medical Microbiology and all physicians working in global health settings. Delegates are welcomed from the UK and worldwide. This year there were delegates from Italy, Belarus, the US, Portugal, Denmark, Germany and Canada.

The course is taught through a series of case presentations as well as didactic teachings. There is also a poster presentation competition and case presentation competition for trainees.

Dr N Beeching presented a case of wound botulism in a young man who uses IV drugs. This case was an excellent reminder that botulism often presents with the 4 D's: dysphagia, dysphonia, diplopia, dysarthria. Additionally, wound botulism may present with atypical features such as fever, decreased level of consciousness, respiratory arrest and does not always follow the typical descending pattern of weakness. Patients who use IV drugs are most susceptible to wound botulism, and the culprit wound must be sought out for debridement.

A case of meningovascular neurosyphilis was covered by Dr N Davies. Neurosyphilis' higher frequency in the post antibiotic era is thought to be due to its partial treatment with antibiotics for other indications, leaving tremponemes in the central nervous system (CNS). Meningovascular syphilis usually manifests 5-12 years after infection and may be associated with prodromal symptoms such as headache, emotional lability and insomnia.

Some zebra cases were presented as well. A case of Acute Necrotising Encephalopathy post Influenza infection was presented by Dr. R. Kneen. The case that stumped the audience was one of paediatric kingella kingae endocarditis causing stroke and osteomyelitis presented by Dr S Hughes. The case presentations competition by trainees included topics such as Whipple's disease and mycotic aneurysm.

The Keynote Richard T Johnson Lecture this year was delivered by Dr Marc Lecuit from the Institut Pasteur, France. He spoke in depth about the microbiology and pathophysiology of listeria invasion into the CNS. Neurolisteriosis is a severe infection, usually manifesting as meningoencephalitis. T-cell suppression such as HIV or medications (infliximab, etanercept) predisposes to neurolisteriosis infection. It is important to remember that listeriosis may not present with sepsis as listeria is not a significantly inflammatory bacteria.

The new 2016 "UK Joint Specialist Societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults" published in the Journal of Infection was covered in depth by Dr F McGill. Key points to remember are that a lumbar puncture (LP) is essential to the diagnosis of meningitis, and that prompt treatment is necessary. Dr U Meyding-Lamade elaborated on steroid use in encephalitis. There is currently insufficient evidence for steroid use in Herpes Simplex Virus (HSV) encephalitis, but preliminary results show that it is likely not harmful.

Dr K Jeffery did an excellent job reviewing the microbiology laboratory aspect of Neuroinfectious diseases. Clinicians should remember to write on requisitions what infectious are postulated (e.g. fungal, anaerobes, TB) because their laboratory work up differs. CSF HSV PCR may be negative in the first several days, thus if clinical suspicion remains LP should be repeated in 3-7 days.

Dr T O'Dempsey and Dr Solomon brought the audience to the global health stage. Dr O'Dempsey shared his experiences working in Sierra Leone during the Ebola outbreak in 2014. The importance of basics such as thiamine was underlined in a young girl who was not recovering after full course of treatment for Ebola and Malaria. Dr Solomon used a case of Zika virus associated Guillain Barre Syndrome (GBS) to review the other infectious aetiologies of acute flaccid paralysis. This includes acute febrile illnesses such as polio, enterovirus 70 and 71, coxsackie virus, echovirus; and post infectious immune mediated damage to peripheral nerves such as acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP). GBS associated with Zika virus infection has a faster onset time from infective illness when compared with garden variety GBS (median 6 days vs 2 months), shorter time to maximal weakness (6 days vs 2 weeks) and more commonly resulting in axonal neuropathy (AMAN/AMSAN) instead of AIDP. Case reports in 2016 have also associated Zika virus with meningoencephalitis, acute myelitis and of course microcephaly.

To date, the Liverpool NeuroID course is the only course worldwide that brings together neurology and infectious diseases. Furthermore, there are several unique ways that this course maximises learning and participation. Trainees are encouraged to participate in friendly competition in case presentations and posters. Most of the talks are delivered via case based presentations to encourage interactive sessions and strengthen retention. The finale of the two days is a challenging "quiz" covering a wide range of topics including talks from the course, historical trivia and other difficult to spot diagnoses. The winner of the quiz gets a snazzy certificate and bragging rights!

The course is approved by The Royal College of Physicians who award 10 CPD credits. In addition there is a very friendly atmosphere with social time built into the agenda; tea breaks elegantly held within the library, dinner at a local restaurant, a 5k "fun run" on the second morning around the city led by Prof Solomon. There was even an award for the delegate who travelled the farthest to attend the course!

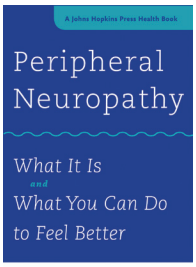
In addition to all the laughter and fun, we were reminded of why we were there with a special book reading from the newly published "Life After Encephalitis" by Ava Easton (www.encephalitis.info/LifeAfterEncephalitis). We heard stories of struggle and recovery and were reminded of our role in helping our patients heal.

For more information:
https://www.liverpool.ac.uk/neuroidcourse

Peripheral Neuropathy: What It Is and What You Can Do to Feel Better

Janice Wiesman, a neurologist with twenty years of experience helping people who have neuropathy find relief, shares her special insights into this painful and debilitating condition. With clarity, Dr Wiesman begins by outlining the basics of nerve anatomy and function. She explains how peripheral neuropathy is diagnosed and treated, describes neuropathy's disparate causes, and offers readers lifestyle changes that can help keep nerves healthy. A useful glossary defines terms, patient stories offer real-world experiences, and illustrations provide a visual key to the condition. A detailed resources section points the reader to reliable web sites and organisations that offer more help.

Concentrating on the most common types of neuropathy, Dr Wiesman provides hope, help, and comfort to patients, families, and carers.



Paperback, 136 pages
ISBN: 9781421420851
November 2016
£14.00
Available from all good retailers

Miratul Muqit receives EMBO YIP Award

Miratul Muqit has been named as one of this year's awardees of the European Molecular Biology Organisation Young Investigator Programme (EMBO YIP). The EMBO YIP awards are among the most prestigious given to young Life Sciences researchers working in Europe, Israel, Turkey and Singapore. Miratul is a Wellcome Trust Senior Clinical Fellow at the MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee and a Consultant Neurologist at Ninewells Hospital. His laboratory is focused on deciphering the fundamental mechanisms of Parkinson's disease and has advanced knowledge on the PINK1 kinase that is mutated in Parkinson's patients. He becomes only the second UK clinician to receive an EMBO YIP after fellow neurologist and clock biologist, Akhilesh Reddy, of the Francis Crick Institute in London.

Charcot-Marie-Tooth awareness film launches first ever video to highlight symptoms of neurological condition

For the first time in the UK, a short-film has been launched to raise awareness of the world's most common inherited neurological condition Charcot-Marie-Tooth (CMT). It aims to spread the word about the condition because so few people have heard of it.

The film has been backed by CMT expert and President of the Association of British Neurologists, Professor Mary Reilly and charity CMT UK, which supports people with CMT, a condition with a wide variety of symptoms including uncontrollable pain, chronic fatigue, unstable ankles, balance problems and falls.

The one minute film – the idea for which came from Douglas Sager (67) who found out he had CMT in 2011 – features people of various ages and at different stages of the condition including Harvey Rogers (10) who has minor nerve damage, his mother Lisa Rogers who has difficulty walking and Emma Lines who is now in a wheelchair and struggles to open a can of pop due to poor co-ordination in her hands. It is interspersed with X-ray style animation so that each person is shown as a digital body of nerves, revealing what can happen when they malfunction.

While CMT is currently incurable, early, accurate diagnosis can improve the lives of those with the condition. Charcot-Marie-Tooth is named after the three scientists who discovered it. Steadily progressive, it causes muscle weakness in the lower legs and hands, leading to problems like hammer toes, restricted mobility, uncontrollable pain and carrying out tasks needing fine motor skills, such as fastening shoe laces. However, people with CMT have a reasonable quality of life with normal life expectancy.

CMT UK's chief operating officer, Karen Butcher said: "Douglas fundraised for this film off his own back and we are delighted with the end result, which is compelling, human and informative. There is so much to tell people about CMT but this captures the bones of it well."

The CMT awareness campaign is being backed by medical professionals including Professor Mary Reilly.

The film was written, produced and directed by award winning film maker and director, Tim Partridge and also has the backing of Shadow Foreign Minister, Catherine West MP.

Catherine said: "I first met Douglas when he came to my constituency surgery and told me about Charcot-Marie-Tooth disease, its problems and lack of awareness about it. It was wonderful to launch the film in Parliament and I hope that it will lead to greater awareness of the cause and symptoms not only in the UK but throughout the world".

To donate visit www.justgiving.com/CMT
To find out more visit www.cmt.org.uk or contact 0800 6526316.

BIAL launches ONGENTYS® (opicapone) a novel treatment for Parkinson's disease patients with motor fluctuations in the UK

ONGENTYS® (opicapone) has been launched in the UK for the treatment of adult Parkinson´s disease patients with motor fluctuations.

ONGENTYS® (opicapone) was authorised by the European Commission in June 2016 as an adjunctive therapy to preparations of levodopa/DOPA decarboxylase inhibitors (DDCIs) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.

Several therapeutic strategies are available to improve the signs and symptoms of Parkinson´s disease, mainly dopaminergic drugs avoiding the degradation or mimicking dopamine physiological effects. Levodopa remains the gold-standard treatment for the disease, although its long-term use causes what is known as motor complications, like end of dose motor complications or wearing-off. "Wearing-off" episodes may be improved with appropriate changes in the medication regimen, i.e. adding an extra dose of levodopa or using a COMT inhibitor.

"There is still an unmet medical need for effective new therapeutic options for Parkinson´s disease. Opicapone will provide clinicians in the UK with a COMT inhibitor, with the convenience of once-daily dosing. It is an option when levodopa-treated patients need additional help to improve motor symptoms such as wearing off in Parkinson´s disease," said Professor Andrew Lees, Professor of Neurology at the National Hospital for Neurology and Neurosurgery, Queen Square, London and University College London.

This news item is based on a press release distributed by Bial and they have paid for its inclusion in ACNR.

IT'S ABOUT GOOD DAYS, NOT LOST DAYS

Please refer to the Summary of Product Characteristics (SmPC) for full details of Prescribing Information

COPAXONE® (glatiramer acetate) 40mg/ml Solution for Injection, Pre-filled Syringe Abbreviated Prescribing Information

Presentation: Glatiramer acetate 40mg solution for injection in 1ml Pre-filled Syringe. **Indications:** Copaxone is indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see Section 5.1 of the Summary of Product Characteristics (SmPC) for important information on the population for which efficacy has been established). Copaxone is not indicated in primary or secondary progressive MS. **Dosage and administration:** Patients should be instructed in self-injection techniques and should be supervised by a healthcare professional the first time they self-inject and for 30 minutes after. A different site should be chosen for every injection. The recommended dose in adults is 40mg of Copaxone (one pre-filled syringe) subcutaneously three times a week with at least 48 hours apart. It is not known for how long the patient should be treated. A decision concerning long term treatment should be made on an individual basis by the treating physician. *Children and adolescents:* No specific studies. *Elderly:* No specific data. *Impaired renal function:* No specific studies. Monitor renal function during treatment and consider possibility of glomerular deposition of immune complexes. **Contraindications:** Known allergy to glatiramer acetate or mannitol. Pregnancy. **Precautions and warnings:** Subcutaneous use only. Initiation to be supervised by Neurologist or experienced MS physician. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Convulsions and/or anaphylactic or allergic reactions can occur rarely. Rarely, serious hypersensitivity reactions may occur. If severe, treat appropriately and discontinue Copaxone. **Interactions:** No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation:** Contraindicated in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Effects on ability to drive and use machines:** No studies have been performed. **Adverse reactions:** Serious hypersensitivity reactions have been reported rarely *e.g.* bronchospasm, anaphylaxis or urticaria. *Very Common:* Infection, influenza, anxiety, depression, headache, vasodilatation, dyspnoea, nausea, rash, arthralgia, back pain, asthenia, chest pain, injection site reactions, pain. *Common:* Bronchitis, gastroenteritis, herpes simplex, otitis media, rhinitis, tooth abscess, vaginal candidiasis, benign neoplasm of skin, neoplasm, lymphadenopathy, hypersensitivity, anorexia, weight increased, nervousness, dysgeusia, hypertonia, migraine, speech disorder, syncope, tremor, diplopia, eye disorder, ear disorder, palpitations, tachycardia, cough, seasonal rhinitis, anorectal disorder, constipation, dental caries, dyspepsia, dysphagia, faecal incontinence, vomiting, liver function test abnormal, ecchymosis, hyperhidrosis, pruritus, skin disorder, urticaria, neck pain, micturition urgency, pollakiuria, urinary retention, chills, face oedema, injection site atrophy, local reaction, oedema peripheral, oedema, pyrexia. Consult the Summary of Product Characteristics in relation to other side effects. **Overdose:** In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted. **Price:** Packs of 12 Pre-filled syringes £513.95. **Legal category:** POM. **Marketing Authorisation Number:** PL 10921/0026. **Marketing Authorisation Holder:** Teva Pharmaceuticals Ltd, Ridings Point, Whistler Drive, Castleford, West Yorkshire, WF10 5HX, United Kingdom. **Job Code:** UK/MED/15/0096. **Date of Preparation:** January 2016.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Teva UK Limited on 0207 540 7117 or medinfo@tevauk.com

UK/UKCPX/16/0015b
Date of Preparation: July 2016