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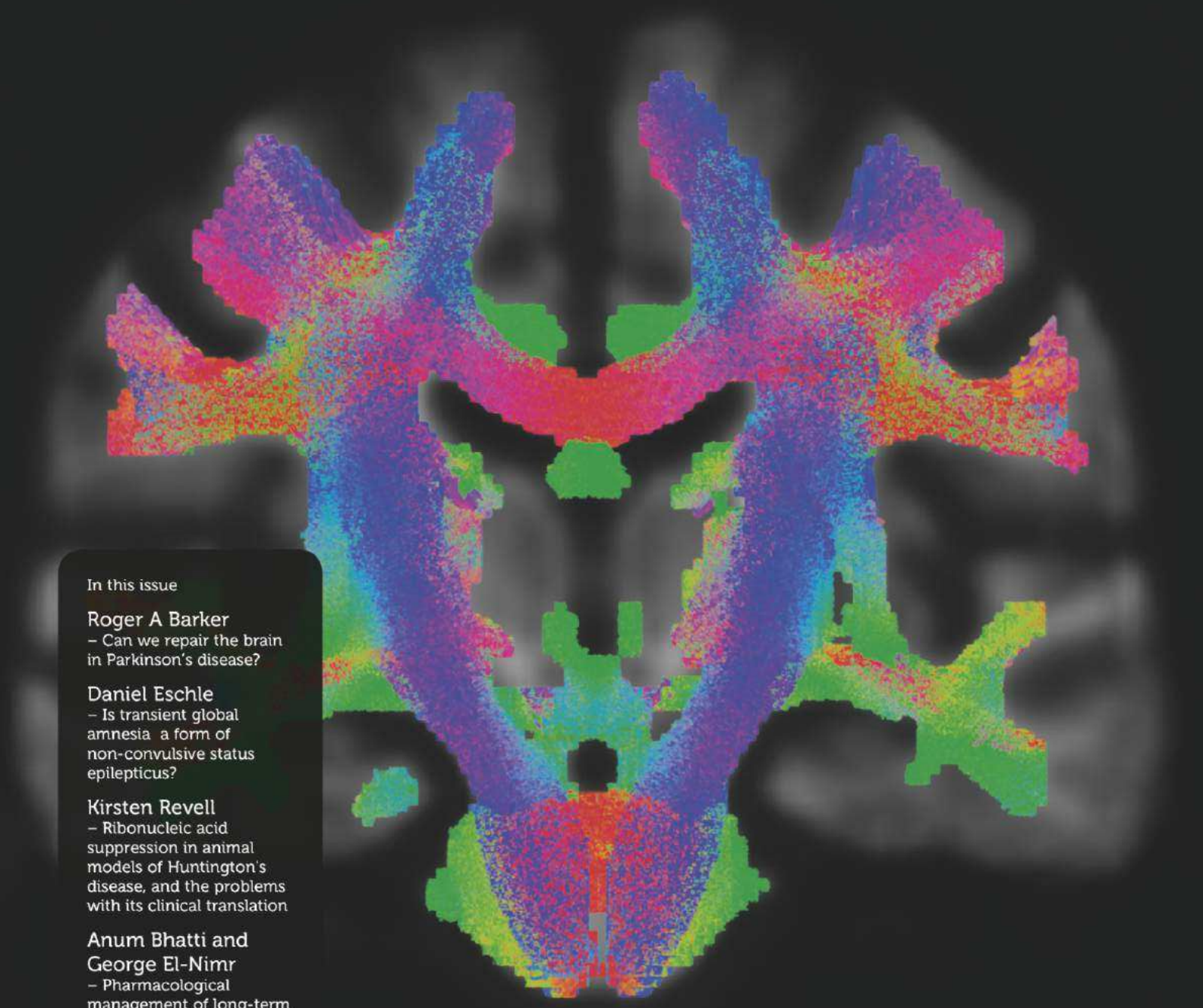
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

PERHAPS IT'S TIME TO TURN TO TAPCLOB

Tapclob, a flexible clobazam liquid antiepileptic drug (AED), can step in to provide additional seizure protection when it's needed most; as an adjunct treatment,[1] as extra cover during cluster seizures,[2] whilst reviewing treatment options[3†] or whilst titrating between first-line AEDs.[3†]

Tapclob® (clobazam) 5mg/5ml and 10mg/5ml Oral Suspension Prescribing Information. See Summary of Product Characteristics (SPC) before prescribing. Presentation: Oral suspension with raspberry odour, containing 5 mg or 10 mg of clobazam per 5 ml of suspension. **Indications:** Clobazam is a 1,5-benzodiazepine indicated as adjunctive therapy in epilepsy. See SPC for details relating to short-term relief of severe anxiety and adjunctive use in schizophrenic or other psychotic illness (including dosing guidance). **Dosage and administration:** *Shake the bottle thoroughly before use. Once titrated to an effective dose of clobazam, patients should remain on their treatment and care should be exercised when changing between different formulations.* ***Treatment of epilepsy in association with one or more other anticonvulsants:*** Start with 20-30 mg/day. Increasing as necessary up to a maximum of 60 mg daily. Re-assess within 4 weeks and regularly thereafter to evaluate the need for continued treatment. A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose. At the end of treatment (including in poor-responding patients), since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended to gradually decrease the dosage. *Elderly and children aged 6 years and above:* Treatment requires low initial doses and gradual dose increments under careful observation. *In children,* start at 5mg daily with a maintenance dose of 0.3 to 1mg/kg body weight daily. **Contra-Indications:** Hypersensitivity to the active substance, benzodiazepines or any of the excipients, history of drug or alcohol dependence, myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic insufficiencies, during the first trimester of pregnancy and in breast-feeding women. Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months and 3 years, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication. **Warnings and precautions:** Amnesia may occur with benzodiazepines. In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines. Special caution is necessary if clobazam is used in patients with myasthenia gravis, spinal or cerebellar ataxia or sleep apnoea. A dose reduction may be necessary. Use with extreme caution in patients with personality disorders. Use of benzodiazepines may lead to the development of physical and psychological dependence therefore the duration of treatment should be as short as possible. Once physical dependence has developed, abruptly stopping treatment will lead to withdrawal symptoms (or rebound phenomena). A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (eg. clobazam) to one with a short duration of action. Monitor respiratory function in patients with chronic or acute severe respiratory insufficiency and consider a dose reduction. In patients with impairment of renal or hepatic function, responsiveness to clobazam and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In long-term treatment renal and hepatic function must be checked regularly. In the treatment of epilepsy, consider that tolerance (decrease in efficacy) may occur. Due to the sorbitol content, do not give to patients with rare hereditary problems of fructose intolerance. The medicine also contains sodium methyl and propyl hydroxybenzoates which may cause allergic reactions (signs include rash, swallowing or breathing problems and swelling of the lips, face, throat or tongue). **Interactions:** At high doses, an enhancement of central depressive effect may occur when used with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anticonvulsant drugs, anaesthetics and sedative antihistamines. Caution if used in patients with lithium intoxication. Alcohol can increase the bioavailability of clobazam by 50%. When adding clobazam to established anticonvulsants, determine the dosage of clobazam by monitoring the EEG and check the plasma levels of the other drugs (e.g. phenytoin, valproic acid, carbamazepine). The effects of muscle relaxants, analgesics and nitrous oxide may be enhanced. If clobazam is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence. Concurrent treatment with drugs that inhibit the CYP P450 system (e.g. cimetidine) may enhance and prolong the effect of clobazam. **Fertility, Pregnancy and Lactation:** Do not use in the first trimester of pregnancy (stop treatment if a woman intends to become pregnant or suspects that she is pregnant). See SPC for risks to the newborn (e.g. 'floppy infant syndrome' and withdrawal symptoms) if administered to the mother during the late phase of pregnancy or during labour. Avoid in breast feeding mothers as clobazam passes into breastmilk. **Effects on ability to drive and use machines:** This medicine can adversely affect the ability to drive and operate machinery. See SPC. **Undesirable effects:** Sedation, leading to fatigue and sleepiness, especially at the beginning of treatment and when higher doses are used. Drowsiness, dizziness or dryness of the mouth, constipation, loss of appetite, nausea, or a fine tremor of the fingers have been reported. These are more likely at the beginning of treatment and often disappear with continued treatment or a reduction in dose. *Paradoxical reactions especially in elderly and in children (discontinue if affected):* restlessness, irritability, difficulty in sleeping, anxiety, delusion, nightmare, hallucinations, suicidal tendencies. In this event, treatment with clobazam must be discontinued. Anterograde amnesia (especially at high doses). Amnesia may be associated with inappropriate behaviour. Respiratory depression (especially at high doses) may occur and is risky for patients with pre-existing compromised respiratory function (i.e., in patients with bronchial asthma) or brain damage. Isolated cases of skin reactions, such as rashes or urticaria, have been observed. Slowing of reaction time, ataxia, confusion and headaches may occasionally occur. Disorders of articulation, unsteadiness of gait and other motor functions, visual disorders (e.g. double vision), weight gain, or loss of libido may occur, particularly with high doses or in long-term treatment, however these reactions are reversible. Unmasking of pre-existing depression. Tolerance and physical and/or psychic dependence may develop, especially during prolonged use. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Abuse of benzodiazepines. When used as an adjuvant in the treatment of epilepsy, restlessness and muscle weakness may occur rarely. As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. Consult SPC for further information. **Overdose:** Induce vomiting (within 1 hour) if the patient is conscious or gastric lavage with airway protection in the patient is unconscious. If this is not beneficial, reduce absorption using activated charcoal. Consider flumazenil as a benzodiazepine antagonist. **Marketing authorisation number and Basic NHS Price:** Tapclob 5mg/5ml PL 00156/0322 (150ml bottle £90.00 and 250ml bottle £150.00). Tapclob 10mg/5ml PL 00156/0323 (150ml bottle £96.00 and 250ml bottle £158.34). **Marketing Authorisation Holder:** Martindale Pharmaceuticals Ltd T/A Martindale Pharma, Bampton Road, Harold Hill, Essex RM3 8UG. **Legal Category:** POM. **Further Information:** Martindale Pharma, Bampton Road, Romford, RM3 8UG. Tel: 01277 266 600. **Date of Preparation:** February 2019

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 Martindale Pharma, an Ethypharm Group Company. Tel: 01277 266 600. e-mail: drugsafety.uk@ethypharm.com

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Date of Preparation: March 2019. CRIT/02/2019/651

† Results from an independent anonymised market research project of 120 Healthcare Professionals funded by Martindale Pharma in November 2015. Data available on request.

Ethypharm

Mike Zandi, Co-Editor

Curing degenerative brain disease has, thankfully, become an ambition of many, but the huge investments (in the billions) and expectations make this an area where rigour of science, peer review and reporting are needed. In this edition Roger Barker (Cambridge) surveys the latest in repair therapies for Parkinson's disease, focusing on cell grafts, the failure of growth factor trials, and the potential promise of induced pluripotent stem cell therapies. Anti-sense oligonucleotide therapy has been one of the major causes for excitement in neurology in the last few years, particularly the story of nusinersen for spinal muscular atrophy, and in the central nervous system the developing story of IONIS-HTTRx in Huntington's Disease, e.g. the recently published Tabrizi et al N Engl J Med 2019 (380:2307-2316 DOI: 10.1056/NEJMoa1900907). Kirsten Revell (Birmingham) decribes RNA biology and the issues, potential pitfalls, and next steps in this area of neuroscience, focusing on Huntington's disease therapy.

Not all effective therapies should cost billions. Nick Ward, Kate Kelly and Fran Brander at Queen Square write on the evidence that high dose and high intensity for rehabilitation is more effective than lower intensity and frequency therapies, with the data focusing on upper limb rehabilitation after stroke. In other articles, Daniel Eschle (Altdorf) takes a considered approach in weighing up the argument that some forms of transient global amnesia (TGA) may have an epileptic origin. The broad differential diagnosis which is discussed in this article demonstrates that giving a diagnosis of TGA alone as a final diagnosis without further thought is clinically risky. Anum Bhatti (Keele) and George El-Nimr (Stoke-on-Trent) review the evidence for the use of drug therapies for the neuropsychological sequelae of traumatic brain injury.

We hope you enjoy this issue of ACNR, which includes the usual diversions, and further short pieces by Andrew Larner on a fictional clinical trial in Arrowsmith by Sinclair Lewis (1885-1951), and an account of Larner's mother's Alzheimer's disease and scrabble playing.

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Mike Zandi, Co-Editor
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BOTOX and MIGRAINE

We read with interest and sympathy Elaine Bell's struggle to find a treatment for her chronic migraine (ACNR 2019;18:20). She is not alone. On the contrary, her story is sadly entirely typical of the 'journeys' made by thousands of chronic headache patients in the UK in search of an effective intervention.

In a recent study of over 200 patients seen for the first time in three secondary and one tertiary care headache clinics in England,[1] the time to referral for expert help was around 10 years and patients had typically consulted their GPs because of headaches on about 10 occasions by the time of referral. Only a third had been given a specific headache diagnosis in primary care – a requisite for appropriate treatment – but about 65% had been referred to a variety of other specialists, very largely inappropriately. All these patients in fact, had 'migraine' but less than half had been offered triptans; and while migraine prophylaxis was indicated this was prescribed in only a minority, often in a haphazard and ineffective fashion. By contrast, compound analgesics and particularly opioid based drugs were used widely and frequently.

The situation in another common headache scenario, post traumatic headache (PTH) following accidental head injury, is still more discouraging. In a recent study, 75% of 109 head and neck injury cases (94% classified as 'minor') developed PTH which persisted in 70% at the time of assessment some two years after injury. The phenotypic diagnosis on evaluation was 'migraine' or 'probable migraine' in 90%; yet 41% had received no treatment at all for this headache problem in primary care.

Despite her long and frustrating search for help, Elaine Bell was at least offered a number of potentially effective treatments and she currently reports ongoing benefit from botox. This treatment has been validated for chronic migraine[3] and is recommended by NICE. There is also now some understanding of its possible mechanism in pain control.[4] In a recent 'real life' prospective study of 254 chronic migraine patients, 94% of whom had failed to respond to or were intolerant of several migraine prophylactics, two thirds showed a significant and meaningful response to botox, notably with twice as many headache free days compared to the pre-treatment state.[5]

While Elaine Bell is quite right in that with regard to the management of chronic migraine there is no "one-size-fits-all" intervention we believe that botox should be considered more often and earlier in the treatment strategy. But more importantly, headache diagnosis and management needs urgent revision in primary care.

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Cover image: "Degenerative disorders of the brain," courtesy of Psychology Press. Buy with 20% discount from https://bit.ly/2EQKvpT

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Dr Andrew Bateman – New Director of NIHR Research Design Service East Of England

Dr Andrew Bateman, Chair of the United Kingdom Acquired Brain Injury Forum (UKABIF) since 2017, is now the new Director of the National Institute for Health Research (NIHR) Research Design Service (RDS) East of England (EoE). Based at the University of Essex, Andrew will combine the role with his appointment as a Reader in the School of Health and Social Care at the University.

The NIHR funds the RDS to provide design and methodological support to health and social care researchers. The RDS aims to increase the quantity and quality of successful grant applications to the NIHR and other national peer-reviewed funding programmes. RDS EoE is one of ten regional services across England and covers the counties of Bedfordshire, Cambridgeshire, Essex, Hertfordshire, Norfolk and Suffolk. With its central office based at the University of Essex, RDS EoE has partner organisations and research advisers at Cambridge University Hospitals NHS Foundation Trust and the Universities of Bedfordshire, East Anglia and Hertfordshire.

Congratulations to our Conference News Editor, Angelika Zarkali who recently won the best poster award from the UCL faculty of brain sciences. This was awarded for her work on hallucinations in Lewy Body disease. Angelika is currently a research Fellow in the Dementia Research Centre at UCL and a Specialist Registrar in Neurology in St George's hospital.

Professor Clive Ballard wins 2019 International Outstanding Achievement Award

Professor Clive Ballard, Executive Dean of the University of Exeter Medical School, was presented with the 2019 Weston Brain Institute International Outstanding Achievement Award in Lisbon, Portugal. This £25,000 award recognises an exceptional researcher who has made significant advances in accelerating the development of therapeutics for neurodegenerative diseases of aging through translational research, has demonstrated remarkable leadership, and has a record of impeccable citizenship in the research community. This year's prize was provided by the Selfridges Group and was open to researchers based in Ireland, the Netherlands, and the United Kingdom.

Congratulations to Janine Barnes who recently received an award from Prince William for her services to Pharmacy and Parkinson's disease at Buckingham Palace. Janine is the founder and Chair of the Parkinson's disease Specialist Pharmacy Network (PDSPN) which aims to educate Pharmacists and their teams in the management of Parkinson's Disease. Read more about the PDSPN on page 9.

Can we repair the brain in Parkinson's disease?

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Parkinson's disease (PD) is a common disorder that typically presents around the age of 70 years with a tremor, slowness of movement and a shuffling gait along with micrographia and a range of non-motor symptoms. The diagnosis is still made clinically and while this turns out to incorrect in a small minority of cases (e.g. the patient has an essential tremor or Multiple system atrophy), this is very unlikely when the diagnosis is made by a movement disorder specialist coupled to an abnormal DaTSCAN and excellent response to dopaminergic medication. Pathologically the condition is characterised by the development of an alpha synuclein pathology at multiple sites in the CNS as well as the enteric nervous system, where many postulate that the disease may begin.[1] Indeed, there is now an emerging school of thought, with some evidence, that PD may start in the gut and olfactory bulb with the misfolding of endogenous alpha synuclein that then spreads and seeds pathology along defined pathways.[2] This would then explain the Braak staging of PD pathology, which was described at the turn of the century, as well as account for the clinical features seen in prodromal or premotor PD.[3] This new pathogenic basis for PD has now led to trials looking at immune therapies/vaccines designed to reduce this spread of pathology and by so doing slow down disease.[4]

While all this is very exciting, the question arises as to whether other approaches for trying to reverse aspects of the PD disease process still have merit – especially those that seek to repair the nigrostriatal dopaminergic pathway – a pathway that has been known to be a key pathological player in PD since the 1960s. This approach, which began in the 1980s, seeks to either replace the lost dopaminergic pathway through the implantation of dopamine cells or the delivery of growth factors to help maintain those cells/fibres that are struggling in the face of the disease process. Both of these approaches are targeted and only deal with one aspect of the disease and are not, and never were seen, as curative. So where do we stand with respect to this strategy in 2019?

The rationale for trying to repair the nigrostriatal pathway

Clearly the best way to treat PD is to diagnose patients at disease onset (before they clinically present with their motor features) and arrest the pathogenic process. This could be through the above approach or using combinations of agents targeting different aspects of the pathological cascade driving the cellular dysfunction and loss in PD, which could include drug repurposing strategies.[5] While all of this is to be encouraged, we also know that restoring dopamine back to normal in early disease with current oral therapies dramatically improves the patient – almost back to normal in the first few years. Of course, with time these treatments start to fail or create side effects – some of which result from stimulation of more intact dopaminergic networks giving neuropsychiatric problems while others come about through non physiological stimulation of the dopaminergic receiving striatal neurons giving dyskinesias. In addition, the disease progresses and affects many other non dopaminergic pathways. Nevertheless, while one reparative treatment cannot stop or help the latter, restoring the dopaminergic nigrostriatal back to a more normal state would negate the need to use the current drugs in PD and all the problems they bring. As such this strategy has the potential to dramatically alter the natural history of treated PD and in theory could mean that all the treatments we currently use for PD become redundant!

Dopamine cell based therapies for PD

In the early 1980s it was shown that the transplantation of foetal dopamine cells from the developing midbrain could survive in the adult rodent brain and restore the animals behaviour largely back to normal when it had been lesioned along the nigrostriatal pathway.[6] This work led by Anders Björklund and colleagues in Lund, Sweden laid the foundation for clinical trials using human foetal ventral mesencephalon (hfVM) at this site led by Olle Lindvall. The first patients in receipt of such tissue did not benefit, but through an iterative process, it was shown to work well in some patients – and more recently this has been extended to show that these grafted cells could survive for up to 24 years with clinical benefits to match.[7] However not all patients improved and even at this time there were concerns about whether this therapy could ever really become a mainline approach in PD given the ethical and practical problems of obtaining such tissue and the inability to standardise it across patients. As a result other cell sources were sought at this time, including adrenal medulla, carotid body, porcine fVM and even engineered retinal pigmentary epithelial cells (Spheramine®), all of which went to clinical trials with no strong signal of efficacy or survival.[8]

However, based on the encouraging results from the Swedish studies using hfVM, other centres took on trialling this therapy and in the 1990s, two NIH funded trials started following the lifting of a federal funding ban on the use of foetal tissue in the USA by President Clinton. These trials were very different in terms of their trial design and execution but both failed to reach their primary end points.[9,10] Following the publication of these trial results in 2001 and 2003 many felt that this marked the end of this cellular reparative approach, while others sought more to reconcile this data with the long term benefits in some of the patients treated in the open label studies.[6] This led to a new EU funded trial, TransEuro, that started in 2010 and which grafted 11 patients between 2015-2018 in the UK and Sweden with a primary end point in 2021 (https://clinicaltrials.gov/ct2/show/NCT01898390).

However, this new trial, while helping to re-establish cellular approaches to PD, still does not get around the ethical and logistical problems of using human foetal tissue. However, this has changed with the development of human embryonic stem and induced

pluripotent stem (iPS) cells and the discovery by Lorenz Studer and Malin Parmar of how to turn such cells into authentic human midbrain neurons.[11,12] This ability to make dopamine cells from such cells has now evolved to the point of clinical trials. The first patient with PD to receive an iPSC derived dopamine cell was reported in November 2018 and other groups and companies are now on the cusp of such trials[13] (https://www.japantimes.co.jp/news/2018/11/09/national/science-health/kyoto-university-performs-worlds-first-ips-cell-transplant-parkinsons/#.XIA2CPZ2u3A).

Even so, the field is still not without risks and controversies including the use of stem cell derived dopamine cells by companies where the pre-clinical data is less convincing.[14] Nevertheless, over the last two years investment in excess of a billion dollars has now gone into this therapeutic approach for PD.

Growth factor based approaches for treating PD

An alternative approach is to try and rescue the remaining dopamine cells/fibres using growth or neurotrophic factors. This has been done around GDNF and the related neurturin using either direct infusions or gene therapies, again with mixed results.

The discovery of GDNF in 1993 and its trophism for dopaminergic midbrain neurons led to the first trial of this agent in the late 1990s when it was directly injected into the cerebral ventricles. This showed no benefits almost certainly because it was unable to get into the brain parenchyma and simply remained in the CSF compartment.[15]

In the early part of this century therefore two groups, one in Bristol led by Steve Gill and the other in Kentucky led by John Slevin sought to directly infuse GDNF into the site of dopamine fibre loss, the striatum, in patients with PD. Both reported success in small numbers of patients,[16,17] which then led to a double blind placebo controlled trial that failed to show any benefits.[18] The reasons for this have been extensively debated and may have included the dose given; the mode of delivery and patient selection. Subsequently this therapy has been trialled again using a new delivery system in Bristol and the results of this trial have just been published.[19,20] The double blind study showed no clinical benefits despite changes on F-dopa scanning while the open label extension phase looked more promising. The reasons as to why this new trial failed will be the subject of further debate, but again patient selection may have been a reason.

The basis for this conclusion comes in part from the work by Ceregene using the GDNF like gene therapy Neurturin. This agent again showed promise in open label studies only to fail in two double blind placebo controlled trials.[21,22] However, pathologically it was shown that in this trial the volume of distribution of the gene therapy was limited and importantly that patients with earlier stage disease had better responses.[23] This would fit with emerging pathological data showing that in the striatum of patients with advancing PD, the number of surviving dopaminergic fibres rapidly declines after about three to five years of motor disease.[24] Furthermore, it has also been shown that alpha synuclein pathology can interfere with the GDNF receptor signalling pathway and that this can be restored through a Nurr 1 pathway[25] – all of which suggests that it may be better to use a dual agent approach in any future trial with GDNF.

In summary, it is still unclear what all this means for future trials of GDNF, although there is still one ongoing in the USA using a gene therapy approach (https://clinicaltrials.gov/ct2/show/NCT01621581). However, it would seem that this agent can have some effect in some PD patients with evidence of target engagement on PET scanning and as such may merit further trials in early stage or even de novo patients.

Conclusion

Strategies to repair the nigrostriatal dopaminergic problems in the PD brain have attracted clinical attention for over 30 years with mixed success. This is in contrast to neuromodulatory approaches using deep brain stimulation and enteral continuous dopamine therapies which have largely shown to work albeit with some complications and limitations.[26] Nevertheless, the logic for what is being pursed with dopamine cell replacement is obvious and has largely failed because of problems of finding reliable cell sources and standardisation of delivery of those cells. This is about to change with the arrival of human pluripotent stem cell therapies, and as such this field will survive or sink in the next five to ten years. As for growth factors for rescuing the dopaminergic network, this has met with less success and the recent trial from Bristol further dampens the reality of this approach, although there may be good reasons as to why this trial failed. However, whether this will lead to a new trial will prove challenging given the many other new approaches that are now been trialled that are designed to target the disease process itself.

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Is transient global amnesia a form of non-convulsive status epilepticus?

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Abstract
Transient global amnesia (TGA) is a clinically defined syndrome of acute hippocampal dysfunction lasting several hours. Its pathophysiology remains elusive, and current hypotheses favour a non-epileptic cause. But hypothetically TGA might share a common mechanism with its closest mimic, namely transient epileptic amnesia. We will look at a few arguments that could explain why TGA is possibly an epileptic phenomenon and maybe even a form of non-convulsive status epilepticus.

Introduction

Consistent with our knowledge of memory formation, transient global amnesia (TGA) is a temporary loss of hippocampal function lasting several hours. Patients, typically between 50 and 80 years of age, are suddenly unable to encode new information, without impairment of attention, self-identity or previously learned skills such as driving or using their phone. The neurological examination is unremarkable. They realise that something is wrong with them, become anxious and repeatedly ask the same questions, as they cannot memorise the answer. The whole episode resolves spontaneously leaving only a memory gap of a few hours.[1] "TGA does not increase the long-term risk of cerebrovascular events, seizures, or cognitive impairment".[2] The chance of re-occurrence is minimal[3] (estimated to be <10% annually), there are no known means of prevention or treatment, and due to its benign nature there is no need for further investigations. Box 1 summarises the clinical TGA criteria based on the work of Hodges & Warlow.[4] Numerous hypotheses regarding pathophysiology have been put forward, but controversy remains and there is no clear winner yet. Imaging data are not consistent with the notion of TGA as a form of transient ischaemic attack (TIA), and the subsequent risk of stroke is not increased. But 'ischaemic amnesia' is an important TGA mimic, and hypothetically TGA might share a common mechanism with another mimic, namely transient epileptic amnesia (TEA), see below. Several studies have found a statistical association between migraine and TGA. Is TGA a form of aura due to cortical spreading depression? But, if so, why do the typical age groups differ, and why are there no other migraine aura symptoms? Venous congestion of the hippocampus due to a Valsalva manoeuvre has also been proposed as a mechanism and emotional or physical factors can trigger episodes, see e.g. Spiegel[1] and Quinette[5] et al for review.

Based on my previous work[5] and further study of the literature on TGA the following questions will be discussed in this paper:

1) Are the Hodges & Warlow[4] diagnostic criteria for TGA specific enough to exclude the risk of missing a mimic such as TEA or ischaemic amnesia?
2) In a comprehensive review of non-convulsive status epilepticus (NCSE), Kinney et al stated that TGA can be readily distinguished from NCSE.[6] Does this statement really apply: Could TGA not be a form of NCSE or maybe a postictal phenomenon?

When trying to answer these questions, we will also look at the role – and limitations – of EEG in the diagnostic process, and discuss the issue of diffusion-weighted MRI (DWI) lesions in the hippocampus due to amnestic episodes.

Two important mimics of TGA

Michel et al[7] published a retrospective case series of patients with amnesia as the predominant presenting symptom. They utilised hospital

Box 1: Diagnostic criteria for transient global amnesia (TGA) according to Hodges & Warlow in JNNP 1990;53:834-843.

- Attacks must be witnessed and information available from a capable observer who was present for most of the attack.
- There must be clear-cut anterograde amnesia during the attack.
- Clouding of consciousness and loss of personal identity must be absent, and the cognitive impairment limited to amnesia, i.e. no aphasia, apraxia, etc.
- There should be no accompanying focal neurological symptoms during the attack and no significant neurological signs afterwards.
- Epileptic features must be absent.
- Attacks must resolve within 24 hours.
- Patients with recent head injury or active epilepsy (i.e. remaining on medication or a seizure in the past two years) are excluded.

records and in particular their large stroke data base (3804 patients at the time) to identify clinical clues that might differentiate certain forms of acute ischaemic stroke and transient ischaemic attacks (TIA) presenting predominantly with amnesia (ischaemic amnesia) from transient global amnesia (TGA).

They identified 13 patients who met their inclusion criteria and also had witnessed episodes. The gold standard for the diagnosis of ischaemic amnesia (as opposed to TGA), was the DWI pattern seen in MRI scans (see below).

In 7 out of these 13 cases it was difficult if not sometimes impossible to distinguish them from TGA on a purely clinical basis. Clues pointing to ischaemic amnesia were: minor additional cognitive signs (executive deficits and mild anomia), minor neurological signs and/or an unusual duration of amnesia (<1 and over 24 hours). During long-term follow-up, cognitive assessment demonstrated persistent amnesia in 4/13 patients. All but 1 of the 13 patients demonstrated DWI lesions distinct from the pattern that is thought to be characteristic for TGA. This one patient demonstrated an isolated hippocampal lesion (20 hours after onset) that "was brighter and more linear than the usual punctuate TGA lesions and showed Gadolinium uptake on repeat MRI at eight days, leading to the diagnosis of ischaemic amnesia". The authors concluded that although ischaemic amnesia could mimic TGA, it is a "rare" occurrence.

But the true rate of underdiagnosis (missing ischaemic stroke or TIA and diagnosing TGA instead) could not be estimated, as less than 25% of the 164 clinically diagnosed TGA patients underwent magnetic resonance imaging with DWI. Given the potential long-term consequences of amnesia, the threshold for an MRI scan with DWI sequences in acutely amnesic patients should be low, particularly in scenarios such as an unusual duration of amnesia, the presence of further cognitive or neurological signs and/or high vascular risk factor load.[7]

Lanzone et al[8] retrospectively analysed clinical and other data of 83 patients with an abrupt occurrence of amnesia that was initially diagnosed as TGA in their emergency department. The aim of the study was to evaluate the accuracy of TGA diagnosis versus the diagnosis of transient epileptic amnesia (TEA) – one of the most relevant TGA mimics. The criteria for TEA according to Zeman[9] are summarised in box 2. All patients received an MRI scan and a standard EEG, and additionally a 24-hour ambulatory EEG, if the standard recording was normal or of borderline significance. Using EEG data and the other Zeman criteria, 15 out of 83 patients (18%) were diagnosed with definite TEA (instead of TGA), and 4 more with possible epilepsy.

Does this mean that every amnesia patient needs an EEG and maybe even an additional 24-hour recording because TEA is such a common TGA mimic? Reading between the lines, it seems that a more thorough history and stricter adherence to established diagnostic criteria could have avoided a number of misdiagnoses and diagnostic procedures (but probably not all). For instance, recurrent amnestic episodes, a duration <1 hour, additional cognitive deficits or onset on awakening were good clues that it was not a case of TGA (but TEA instead).

These two case series illustrate once again that despite the unknown pathophysiology of TGA, the diagnostic criteria are quite robust and helpful in recognising mimics that do not have such a benign prognosis. However, they do not exclude all cases with an ischaemic or epileptic aetiology, and these alternative diagnoses should always be considered.

Box 2: Diagnostic criteria for transient epileptic amnesia (TEA) according to Zeman et al in JNNP 1998;64:435-443.

- There was a history of recurrent episodes of transient amnesia.
- Cognitive functions other than memory were judged to be intact during typical episodes by a reliable witness.
- There was evidence for a diagnosis of epilepsy by: EEG, co-occurrence of other seizure types and/or a clear-cut response to anticonvulsant medication.

Box 3: Differential diagnosis in acute amnesia according to Bartsch & Butler in Nat Rev Neurol 2013;9(2):86-97.

- **Transient global amnesia (TGA):** see box 1
- **Transient epileptic amnesia (TEA):** see box 2
- **Transient ischaemic attacks (TIA):** additional cognitive or neurological signs (see main text for further information)
- **Psychogenic amnesia:** persistent retrograde amnesia with loss of self-identity as a 'defence' against a criminal offense or trauma
- **Delirium:** acute 'amnesia' in the context of impaired attention ± pre-morbid impairment of cognition
- **Dementia:** (slowly) progressive amnesia ± other cognitive deficits corroborated by relatives or other witnesses
- **Depression:** subjective feeling of impaired memory dominates
- **Korsakoff syndrome:** history of malnutrition ± signs of Wernicke encephalopathy with ataxia, opthalmoplegia and confusion
- **Herpes simplex encephalitis:** initially headache, fever and confusion with chronic anterograde amnesia in the aftermath
- **Limbic encephalitis:** subacute amnesia, behavioural changes and/or seizures (autoimmune pathophysiology)
- **Traumatic brain injury:** signs of head injury
- **Drug effects:** history ± positive toxicology screening for benzodiazepines or opioids (consider antidotes to confirm)
- **Amnesic shellfish poisoning:** history of shellfish consumption with initial 'food poisoning' followed by amnesia

MRI in TGA

Numerous case series have established that the MRI hallmark of TGA are singular 'punctate' uni- or bilateral hippocampal DWI lesions that are most common 24-72 hours after onset – at a time when the symptoms have already resolved. These specific hippocampal lesions were rarely seen in the hyperacute phase (2/31), "but all became visible regularly at 48 hours" in 26 of 31 TGA cases in a seminal paper on this topic.[10] DWI lesions outside the hippocampus, not 'punctate' and/or not delayed (<24 hours) are most likely of ischaemic origin.[11] All lesions, in TGA or ischaemia, should be mirrored by a corresponding signal in the ADC sequences. The hippocampal location of these DWI lesions in TGA should not come as a surprise. The hippocampus is basically the cornerstone of memory formation. But how do we explain the delayed appearance 24-72 hours after onset? Clearly, this sets TGA apart from lesions of ischaemic origin that appear within a few hours (at most). DWI lesions reflect – in simplified terms – a disruption of cellular osmotic homeostasis and are potentially reversible, if the triggering factor is reversed fast enough. We could hypothesise that the mechanism (at present unknown) triggering amnesia, also triggers some form of inhibitory mechanism that reverses the amnesia, but does not stop soon enough and so temporarily leads to a disruption of osmotic homeostasis and hence a delayed DWI lesion (which is small enough 'to be seen but not heard'). This scenario is akin to what we can postulate for Todd's paresis and leads up the next section.[12]

Could transient global amnesia be an epileptic phenomenon?

There are several theories regarding the pathophysiology of TGA, but none has stood the test of time (yet).[1] The currently employed diagnostic criteria are an empirical construct that does not reflect a particular pathophysiology (but implies a particularly good prognosis).[4] So, could transient global amnesia be an epileptic phenomenon? If the answer is 'yes', then it might actually be a benign form of NCSE.

There are several case series that reported a lack of epileptiform activity in standard EEG recordings during and after episodes of TGA.[3] A 'standard' EEG is a surface recording that lasts about 20 minutes. Although this method has excellent specificity (94.7%), its sensitivity is very low (17.3%) as defined by the presence of epileptiform activity.[13] One reason is the duration of the EEG. Sensitivity increases with longer recordings, e.g. 53.3% epileptiform abnormalities in standard versus 100% for the 24-hour EEG in the case series of Lanzone.[8] Another reason is that epileptiform

activity in many cases literally stays below the surface: "90% of cortical spikes with a source area of >10cm² produced scalp EEG spikes, whereas only 10% of cortical spikes having <10cm² of source area produced scalp potentials. Intracranial spikes with <6cm² of area were never associated with scalp EEG spikes".[14] So, all in all, a normal 'standard' EEG would not necessarily exclude epileptic activity in the hippocampus during TGA.

We also have to consider the possibility that the disruption of memory formation is due not to ongoing epileptic activity, but rather a post-ictal phenomenon with a normal EEG. The following case report[15] might point in that direction: "a brief (<1 minute) burst of left temporal spikes, during which the patient was unresponsive to speech, was followed by normalisation of the EEG and a 10-minute period of amnesia characterised by repetitive questioning about recent events".

Conclusions

There are (a few) important TGA mimics, see box 3.[16] Strict adherence to diagnostic criteria, i.e. painstakingly excluding cognitive deficits beyond pure amnesia and minor neurological abnormalities, will help to identify mimics such as stroke, TIA or TEA. It cannot be stressed enough – in the opinion of this author – that the term 'transient global amnesia' is not a generic label that can be applied to every and any amnestic episode. In many older case reports[17] the patients actually suffered from what we now call 'transient epileptic amnesia' instead of TGA (see boxes for distinct diagnostic criteria). There are some factors beyond the diagnostic criteria that have to be kept in mind: Mild headache, dizziness or nausea/vomiting are not exclusion criteria for TGA, and a certain degree of temporary retrograde amnesia is typical.[4] In patients younger than 50 and older than 80 years of age, those with recurrent attacks, atypical duration of amnesia (<1 and longer than 24 hours) and/or episodes on awakening, other differential diagnoses than TGA have to be considered.[3] As the duration of TEA and TGA does not always differ significantly (e.g. a median of three for TEA versus four hours for TGA in Lanzone[8]), the distinction between the two becomes more challenging after a first episode. If there is uncertainty regarding a diagnosis of TGA, then obtain an MRI as soon as possible (do not bother with a CT scan) to exclude non-characteristic DWI and other lesions. An EEG has to be ordered in some cases, but bear its low sensitivity in mind.

In conclusion, the pathophysiology of TGA remains unknown. A benign ictal (NCSE) or a post-ictal phenomenon should be considered as possible causes.

But questions remain: At present, we do not know enough about possible 'subtypes' of TGA.[18] Is TGA different if we see a right- instead of left-sided DWI lesion? In clinical practice we unwittingly test hippocampal function of the dominant hemisphere when evaluating TGA patients, because we primarily judge retention of verbal information. But we should always try to include a visuospatial (non-verbal) task to test the contra-lateral hippocampus: Have the patient copy a geometric design, and test at regular intervals whether (s)he can reproduce it from memory.

Also, the putative TGA mechanism would have to account for a way to explain bilateral DWI lesions in some cases and why it usually occurs only once, something we would not necessarily expect in focal hippocampal seizures or a mechanism akin to Todd's paresis. – The search and debate will have to continue.

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Ribonucleic acid suppression in animal models of Huntington's disease, and the problems with its clinical translation

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Abstract
Huntington's disease (HD) is an autosomal dominant, progressive, neurodegenerative disorder; most commonly affecting adults.[1] A mutant expansion of a CAG repeat >36 copies on chromosome 4, coding for the Huntingtin protein (HTT), underlies numerous downstream cellular pathologies. Using murine models that carry the mHTT gene, anti-sense oligonucleotides (ASOs) have been identified that can reduce the progression of signs in affected mice; one of which has now been translated into human trials. Many researchers maintain that the huge variation between human and murine genomes, behaviour and complexity means that treatments cannot be readily translated between the two species. Many similarities have been found between the nucleotide structure of murine and human HTT genes, allowing for both viable transgenic mice and translatable ribonucleic acid (RNA) therapies to be developed.

A mutant expansion of a CAG repeat >36 copies on chromosome 4, coding for the abnormal Huntingtin protein (HTT), leads to numerous downstream cellular problems; culminating in cell death including the striatal medium spiny neurons.[2] Development of murine HD models has allowed for the investigation of RNA targeting treatments,[3] that have subsequently been the subject of both primate and human safety trials. Use of these models has facilitated advances in the development of both allele non-specific and allele specific approaches to gene suppression, including the first human trial.[4] This review discusses current RNA treatments in HD and the issues that complicate their translation from animal models to human trials.

This review is a summary of present knowledge and does not set out to evaluate efficacy of potential treatments, and therefore the specific methodology of animal research is not evaluated here. However, studies using animal models of Huntingtin mRNA suppression with salient results for human application are outlined; followed by an evaluation of murine models of HD and the issues each presents with translating treatment options into humans.

1. Method

To source trials for this literature review, Cochrane CENTRAL and Google Scholar were independently accessed, and a computerised search was undertaken. Results were processed in line with PRISMA guidelines.[5] Table 1 describes the search protocol for RNA suppression and Table 2 describes the search protocol for animal models of HD.

2. Results

Table 3: Eligibility screen for RNA suppression.

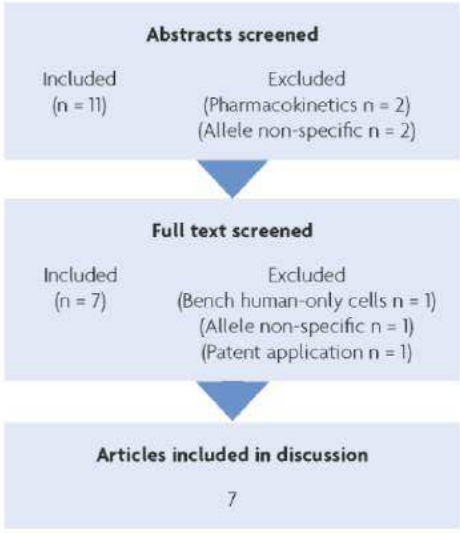

Table 4: Eligibility screening for animal HD models.

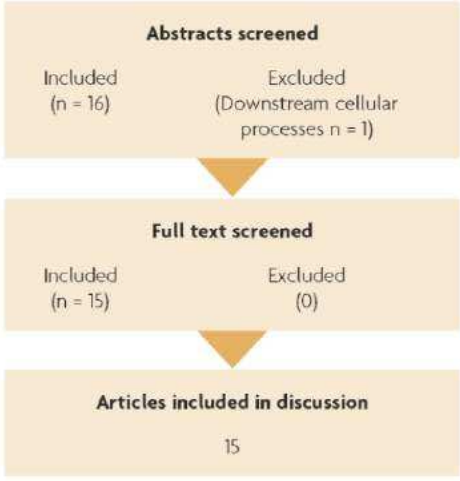

Table 1

Step	Database	Search Term	No. Results	
1	**Cochrane Central**	"oligomer RNA suppression in huntington" "oligomer suppression huntingtin"	0 0	
2	**Google Scholar, PubMED/MEDLINE**, ScienceDirect (Elsevier), Ovid	"oligomer RNA suppression in huntington" "oligomer RNA suppression huntingtin"	5 2	
3	›› cited by (5)		1	
4	›› Mendeley (Wiley)	Related articles	11	
5	›› ScienceDirect	Related articles	2	
			21	
				Exclusion Criteria
6			-4	Duplicates
7			-3	Unrelated
8			-1	Book chapter
9			-2	Pre 2010
		Total for eligibility review	**11**	

Table 2

Step	Database	Search Term	No. Results	
1	**Cochrane Central**	"RNA Huntington"	3	
2	›› Karger	Related articles	2	
3	›› Mendeley (Wiley)	Related articles	11	
4	**Google Scholar, PubMED/MEDLINE**, ScienceDirect (Elsevier), Ovid	"murine Huntington's" "murine huntingtin"	14 7	
5	›› cited by (74)		2	
6	›› Mendeley	Related articles	15	
			55	
				Exclusion Criteria
7			-24	Duplicates
8			-15	Unrelated
		Total for eligibility review	**16**	

3. RNA Suppression

The disease phenotype of HD is generated by toxic accumulation of mutant HTT (mHTT) in neurons including the medium spiny neurons of the striatum, as well as accompanying glial cells. This mutant protein has a defective tertiary structure due to excessive replication (>36) of a cytosine-adenine-guanine (CAG) sequence within exon 1 of the gene.[2] Due to the autosomal dominant nature of HD, patients also have an unaffected allele which codes for wild-type HTT (wtHTT).

RNA suppression works by introducing short strands of nucleotides that complement segments of mRNA coded for by a gene; binding to them and, through one of several mechanisms, preventing them from being translated into protein. These strands are called antisense oligonucleotides (ASO). Many disorders can be treated using SC or IV introduction of water-soluble oligonucleotides; using sugar backbones as a vector for transport into the cell.[5] Oral administration of second generation ASOs is also possible utilising permeation enhancers such as sodium caprate, with acceptable resultant levels of plasma bioavailability.[7] However, the resulting molecules are often incapable of being transported across the blood brain barrier; so for HD, short stranded oligonucleotides are injected directly into the CSF of the affected subject where they are taken up by neural cells.[6]

To study the potential use of ASOs in HD, murine models of HD were used which were first generated shortly after the gene was discovered in the mid-1990s. There are three main types of murine HD homolog: Transgenic mice, knock-in mice and YAC/BAC mice.[2] Transgenic mice carry two natural copies of murine wtHTT gene, in addition to the inserted copy of exon 1 of human mHTT gene on a random locus of their genome; thus producing both wtHTT and mHTT as well as displaying an HD phenotype.[3] Knock-in mice have the expanded CAG repeat inserted into their existing murine HTT gene and so produce only mHTT.[3] Lastly, YAC/BAC mice have the full human HTT gene introduced into their cells via yeast or bacterial DNA and so, like transgenic mice, also produce both forms of HTT.[3]

Historically, RNA suppression treatments have focused on inhibiting both wtHTT and mHTT production using nucleotide sequences from exons on the 5' end of resulting mRNA. Using phosphorothioate modified oligonucleotides that catalyse RNase degradation of HTT mRNA, this has been demonstrated to be effective in reducing abnormal signs in HD transgenic mice; not only during treatment but for an extended period after final administration of the ASO.[8] Currently the ASO identified by Kordasiewicz and colleagues is the only HTT-suppressing drug to have completed stage 1 human trials and is currently being developed for bigger phase II clinical trials (please see section 4 for further discussion).

However, wtHTT is essential for normal

neural development and health, including in CREB (and therefore BDNF) production, mitochondrial energy conversion and other essential cell processes.[9,10] More recent research has therefore focused on identifying potential ASOs that are allele specific to mHTT.[11]

Gagnon et al (2010)[12], Skotte et al (2014),[13] Rue et al (2016)[14] and Datson et al (2017)[15] all identified potentially therapeutic, allele specific, locked nucleic acid-modified ASOs (LNA-ASO), targeting the mutant length CAG repeats in mHTT mRNA; whilst sparing both wtHTT and other CAG repeat-containing genes in transgenic mice. These ASOs also did not catalyse RNase and furthermore multiple ASO strands worked in conjunction on very large CAG repeats, indicating disruption of translation as the mechanism of action.[12,14] Likewise; Carroll et al[15] identified LNA-ASOs capable of selectively binding to SNPs on segments of mHTT mRNA in YAC/BAC mice. In each case, administration displayed benefits in terms of the progression of signs in these transgenic, knock-in or YAC/BAC mice.

Miniarikova et al (2016)[16] created four expression cassette-optimised artificial microRNAs (miRNA) targeting human HTT exon 1 (miH), the expanded CAG repeats (miCAG), C or T isoform of SNP rs362331 in exon 50 (miSNP50C and miSNP50T) and the T isoform of SNP rs362307 in exon 67 extended to 3'UTR (miSNP67T). Complete silencing of wtHTT and mHTT was achieved targeting exon 1 and miCAG. mHTT specific silencing was achieved targeting the heterozygous SNP rs362331 in exon 50 or rs362307 in exon 67.[16]

Sun et al (2014)[17] identified a phosphorodiamidate morpholino oligonucleotide (PMO) capable of selectively suppressing mHTT mRNA. PMOs have the benefit of being a particularly stable, soluble and non-toxic type of ASO. The study found CAG repeat-targeting PMOs, with one strand being able to suppress mHTT in both transgenic and knock-in mice.[17]

4. Translating animal HD models to humans

Each type of murine HD model comes with its own issues in terms of how the results from them can be translated to clinical studies.

Transgenic mice such as R6/1 and R6/2 have a tendency to show severe signs consistent with an HD phenotype early in life.[18] This allows for good comparison to juvenile HD as well as rapid screening of treatments for clinical effects. Likewise, YAC mice show early cellular changes reflecting those of human HD.[19] Whilst both types of mice show the characteristic progressive phenotype, the issue remains that they do not represent a direct genetic correspondent of human HTT production.[3] The addition of human mHTT alleles, or segments thereof, into a random locus of the murine genome means HTT mRNA is not being produced by this gene in its natural locus. In R6/2 mice, the addition of the transgene causes a coincident deletion of the Gm12695 gene; causing expression of a partial fragment. Such expressions displayed by this model cause changes in a range of cell processes such as synaptic transmission and cell signalling.[20] However, we are not yet fully aware of all linkage relationships with HTT and consequent protein production or downstream mediation in either mice or humans, which poses a potentially major issue in terms of efficacy and safety. In addition, the presence of the human HTT gene may interfere in a linkage manner with the expression of other unrelated murine genes.[2]

Knock-in mice such as HdhQ9221 or CAG140/15022 more closely resemble naturally occurring HD in humans, as segments of human mHTT gene are inserted into the existing locus of the murine HTT gene. This means that the mice display a genotype with one mHTT gene and one wtHTT gene, like most human subjects.[23] Whilst this allows for a more natural development of cell pathology, behavioural correlates are less pronounced and variation in mortality is not reliably useful as a measure for research trials.[2,3]

In a broader sense, many researchers maintain that the huge variation between human and murine genomes, behaviour and complexity means that treatments cannot be readily translated between the two species. Certainly, the effects of introducing a CAG repeat that is much longer than the one naturally occurring in mice does not necessarily create the same changes seen in humans. In one study, an increase in CAG repeat to a super-long size created a paradoxical increase in life expectancy of affected mice, directly contradictory to the human phenotype.[24] However, whilst these are all valid criticisms, many similarities have been found between the nucleotide structure of murine and human HTT genes,[25] allowing for translatable RNA strands to be developed.

Trials in more complex animals, with genomes and characteristics that more closely resemble humans, is essential before human trials can be conducted but brings with it issues of cost and numbers of animals that can, and should, be treated pre-clinically.

To date, this has been attempted through the development of both ovine and porcine HD models. Transgenic sheep injected with full-length human mHTT gene containing 73 CAG repeats have shown expression of mHTT and abnormalities in medium spiny neurons. However, these transgenic sheep show no overt phenotype at later stages of development.[26]

In pigs, trinucleotide repeat lengths more closely resemble those of humans; with CAG repeats of up to 21 identified in the porcine HTT allele.[27] Minipigs have been identified as a suitable transgenic HD model, as their physiology resembles that of humans in several respects. They have a large brain suitable for imaging and there is 96% homology between porcine and human HTT genes. Similar to ovine models, transgenic pigs have historically showed abnormalities of striatal structures, but did not display any behavioural correlates or overt phenotype.[28] However, progress with porcine models has been made recently with a knock-in porcine HD model that displays consistent abnormalities reflective of human HD.[29] These pigs also show selective degeneration of striatal medium spiny neurons and the incorporated CAG repeat extension is germline transmissable. This model represents the most analogous model of human HD in a large mammal to date and provides a promising platform for treatment trials.

Likewise, no naturally occurring HD homolog exists in non-human primates. Currently, trials to establish the safety of reducing wtHTT in adult primates (in line with the Kordasiewicz (2012) study)[8] have been conducted and the impact of ASO reduction of wtHTT was found to have no adverse effects; with the exception of a temporary loss of knee reflexes in monkeys, which may be more associated with the mode of delivery than the therapeutic agent itself.[30] It may soon be possible to emulate HD in non-human primates via one of two methods: hyperexpression of mHTT activated by viral vectors (Ramaswamy et al., 2007),[2] or using transgenic rhesus macaques carrying the mutant exon-1 of human IT15 (Yang et al., 2008).[31]

Whilst the treatment option currently being studied in a human trial (IONIS HTTRx) developed from the findings of Kordasiewicz and colleagues (2012)[10] provides a promising option for adults with HD, with no adverse reported events to date, its lack of specificity for mHTT does mean it may need modifying or an alternate, allele specific ASO developed. This is particularly true for juvenile HD, in which inhibition of wtHTT may have significant (and incompletely known) effects for patients. Given this, one would predict that a focus on allele specific PMOs or LNA-ASOs will eventually take precedence in HD research. Genetic variability and further understanding of the different genotypes and phenotypes of HD will inevitably provide avenues for treatment development, such as that of Skotte and colleagues (2014);[13] but also complications for developing mHTT specific ASOs effective in all HD variants.

Conclusion

RNA suppression works through the introduction of ASOs into the CSF that either inhibit HTT mRNA translation or catalyse HTT mRNA degradation. This process can be allele specific to mHTT mRNA, or non-specific affecting both mHTT and wtHTT production. Using murine models that carry the mHTT gene, ASOs have been identified that are able to reduce signs in affected mice; and one of these therapies has now been the subject of a clinical trial in patients with HD. Issues exist when translating findings from murine models to human patients. Work in primate and other large animal models of HD may gain greater prominence in the years to come; with promising models having emerged last year.

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NASA delegation visits University of Birmingham to discuss its mission to Mars

NASA scientists and astronauts have visited the University of Birmingham to discuss how drug discoveries in NHS patients could reduce brain pressure during space travel to allow them to go beyond the Moon. One of NASA's missions is to see the first humans set foot on Mars, however microgravity – which causes astronauts to float in space – can have significant physiological effects on the body and can lead to pressure on the brain that can cause visual impairment.

Astronauts would spend months in microgravity travelling to and from the Red Planet, therefore NASA's scientists need to find a solution to prevent this intracranial pressure.

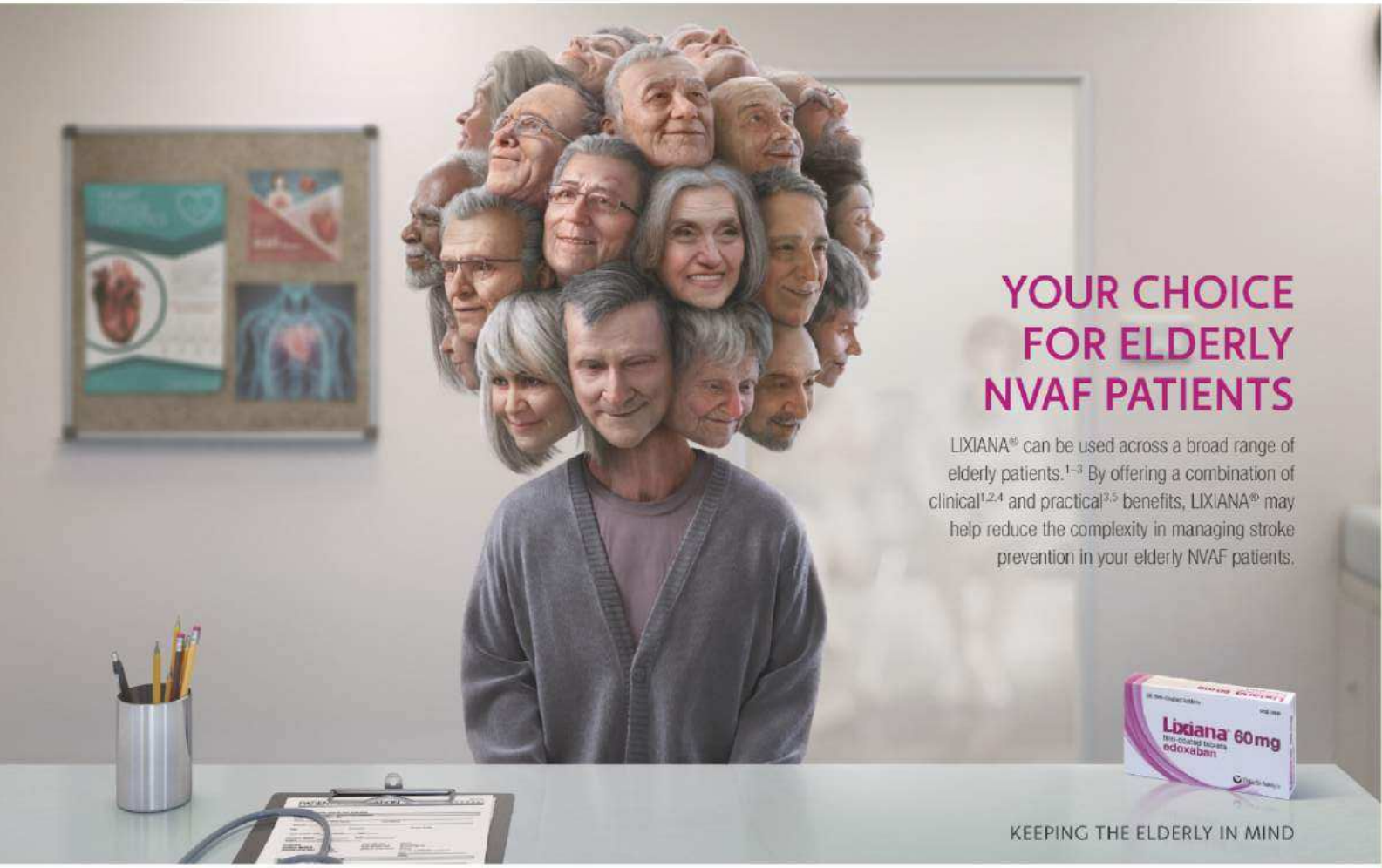
A delegation from NASA held round-table talks with Dr Alex Sinclair and her research group at the University of Birmingham to learn more about their research into a condition called Idiopathic Intracranial Hypertension (IIH) which has similar effects on the body as the brain pressure caused by space travel.

NIHR Clinician Scientist Fellow Dr Sinclair is also a consultant neurologist at University Hospitals Birmingham NHS Foundation Trust, leading one of the world's largest IIH clinical services based at Queen Elizabeth Hospital Birmingham.

By combining clinical neurology with translational research, Dr Sinclair and her team are now world leading experts in brain pressure.

Daiichi-Sankyo

Lixiana® edoxaban



LIXIANA® is a once-daily direct oral anticoagulant (DOAC) indicated for:

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

In NVAF patients with high CrCl, there is a trend towards decreasing efficacy with increasing CrCl for edoxaban vs well-managed warfarin, therefore careful evaluation of thromboembolic and bleeding risk is necessary before initiation.

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LIXIANA▼ (edoxaban) 60 mg / 30 mg / 15 mg film-coated tablets prescribing information

Refer to the Lixiana Summary of Product Characteristics (SmPC) prior to prescribing

Presentation: 60 mg (yellow) / 30 mg (pink) / 15 mg (orange) edoxaban (as tosilate) film-coated tablets. **Indications:** Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **Posology and method of administration:** *NVAF:* Recommended dose is 60 mg edoxaban once daily with or without food. Continue therapy long term. *VTE:* Recommended dose is 60 mg edoxaban once daily with or without food following initial use of parenteral anticoagulant for at least 5 days. Duration of therapy (at least 3 months) should be based on risk profile of the patient. For NVAF and VTE the recommended dose is 30 mg edoxaban once daily in patients with one or more of the following: moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 mL/min); low body weight ≤ 60 kg; concomitant use of the P-glycoprotein (P-gp) inhibitors, ciclosporin, dronedarone, erythromycin, or ketoconazole. The 15 mg dose of edoxaban is not indicated as monotherapy, and should only be used during a switch from edoxaban to VKA in certain patients (see SmPC for full details). Edoxaban can be initiated or continued in patients who may require cardioversion. For transoesophageal echocardiogram guided cardioversion in patients not previously treated with anticoagulants, edoxaban should be started at least 2 hours before cardioversion to ensure adequate anticoagulation. Cardioversion should be performed no later than 12 hours after the dose of edoxaban on the day of the procedure. Confirm prior to cardioversion that the patient has taken edoxaban as prescribed. If a dose of edoxaban is missed, the dose should be taken immediately and then continued once daily on the following day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition, if considered to be a significant risk for major bleeding including current or recent gastrointestinal (GI) ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Uncontrolled severe hypertension. Concomitant treatment with any other anticoagulants e.g. UFH, low molecular weight heparins, heparin derivatives (fondaparinux, etc.), VKA or DOACs except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. Pregnancy and breast-feeding. **Special warnings and precautions for use:** *Haemorrhagic risk:* Caution in patients with increased risk of bleeding such as elderly on ASA. Discontinue if severe haemorrhage occurs. The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for edoxaban is not available. Haemodialysis does not significantly clear edoxaban. *Renal impairment:* CrCl should be monitored at the initiation of edoxaban and afterwards when clinically indicated. Not recommended in patients with end stage renal disease or on dialysis. *Renal function and NVAF:* A trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high CrCl after a careful benefit risk evaluation. *Hepatic impairment:* Not recommended in severe hepatic impairment. Caution in mild or moderate hepatic impairment. Caution in patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN. Perform liver function testing prior to initiation and then periodically monitor for treatment beyond 1 year. *Surgery or other interventions:* discontinue edoxaban as soon as possible and preferably at least 24 hours before the procedure. If procedure cannot be delayed, the increased risk of bleeding should be weighed against urgency of the procedure. Restart edoxaban as soon as haemostasis achieved. *Prosthetic heart valves and moderate to severe mitral stenosis:* Not recommended. *Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy:* Not recommended. *Patients with active cancer:* Not recommended in treatment and/or prevention of VTE. *Patients with a history of thrombosis diagnosed with antiphospholipid syndrome:* DOACs including edoxaban are not recommended. **Drug interactions:** Concomitant use of the *P-gp inhibitors* ciclosporin, dronedarone, erythromycin, or ketoconazole requires edoxaban dose reduction to 30 mg. Edoxaban should be used with caution with concomitant *P-gp inducers* (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort). Concomitant high dose ASA (325 mg) or chronic NSAIDs is not recommended. Concomitant ASA at doses > 100 mg and < 325 mg should be under medical supervision only. Very limited experience with dual antiplatelet therapy or fibrinolytics. Possibility of increased bleeding risk with concomitant SSRIs or SNRIs. **Adverse reactions:** *Common:* anaemia, dizziness, headache, epistaxis, abdominal pain, lower GI haemorrhage, upper GI haemorrhage, oral/pharyngeal haemorrhage, nausea, blood bilirubin increased, gamma GT increased, cutaneous soft tissue haemorrhage, rash, pruritus, macroscopic haematuria/urethral haemorrhage, vaginal haemorrhage, puncture site haemorrhage, liver function test abnormal. *Serious uncommon:* thrombocytopaenia, hypersensitivity, intracranial haemorrhage (ICH), intraocular haemorrhage, other haemorrhage, haemoptysis, surgical site haemorrhage. *Serious rare:* anaphylactic reaction, allergic oedema, subarachnoid haemorrhage, pericardial haemorrhage, retroperitoneal haemorrhage, intramuscular haemorrhage (no compartment syndrome), intra-articular haemorrhage, subdural haemorrhage, procedural haemorrhage. **Legal classification:** POM. **Package quantities, marketing authorisation (MA) numbers and basic NHS costs:** 60 mg – 28 tablets – EU/1/15/993/018 - £49.00. 30 mg – 28 tablets – EU/1/15/993/005 - £49.00. 15 mg – 10 tablets - EU/1/15/993/001 - £17.50. **MA holder:** Daiichi Sankyo Europe GmbH, Zielstattstrasse 48, 81379 Munich, Germany. **Date of preparation of Prescribing Information:** May 2019. 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Pharmacological management of long-term aggression secondary to traumatic brain injuries

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Abstract
Aggression is common after traumatic brain injuries (TBI) in acute and chronic settings. However, there is limited guidance regarding its assessment and effective management. Whilst a number of pharmacological options are available for long term treatment, the evidence base is not of an adequate strength to support a unified practice. This article will explore the currently available guidelines and recommendations for treating chronic aggression after TBIs and evaluate the evidence for its pharmacological management.

Introduction

Aggression is a long term neurobehavioural sequelae of TBIs with incidences quoted from 11.5-33.7%.[1] In TBI patients, aggressive behaviour tends to be impulsive rather than premeditated and can manifest as episodic dyscontrol syndrome, disinhibition or exacerbated premorbid antisocial traits.[2] The underlying mechanisms of aggression are complex allowing numerous and diverse interventions targeting various pathways.

In acute settings, Lombard and Zafonte (2005) describe non-pharmacological measures to manage aggression including environmental alterations and ensuring minimal or non-contact restraints. Screening for systemic causes, optimising pain control and patients' sleep-wake cycle are also advocated. In the event of failed non-pharmacological treatment, Lombard and Zafonte (2005) recommend that medication choice should be tailored to individuals; with side effect profiles taken into consideration.[3]

For chronic aggression, psychological therapies are used as a first line with pharmacological interventions trialled in later stages.[4] Psychological therapy options include cognitive behavioural therapy (CBT), behavioural management utilising operant learning theory and contingency management. However, a review by Alderman (2013) concluded that further evidence using scientific methods is needed to analyse these approaches.[5] Comparatively, there is a diverse body of literature addressing long term pharmacological treatment although quality among studies are varied. This article will focus on the aetiology for chronic post TBI aggression, current management guidelines and the evidence for long term pharmacological interventions.

Aetiology

Post TBI aggression has been associated with lesions affecting the prefrontal cortex – particularly the orbitofrontal and ventromedial areas – causing a loss of behavioural regulation. Disruption to inhibitory pathways between the prefrontal cortex and limbic system also results in limbic kindling and inappropriate emotional responses to negative stimuli thus facilitating aggressive behaviour.[2] Associated neurotransmitter abnormalities include low cortical serotonin and impaired gamma amino-butyric acid (GABA)/ glutamate levels.[6] Altered catecholamine and cholinergic levels are associated with cognitive impairment[2] thus distorting information processing and predisposing patients to aggression.[6] In TBI patients, underlying anxiety, affective disorders, seizures and frontal lobe dysfunction also increase susceptibility.[10]

Differentials for aggression

When identifying a cause for chronic aggressive behaviour, a patient's previous experiences, comorbid psychiatric conditions and alcohol and/ or substance abuse must be established with a collateral history.[2,7] McAllister (2008) highlights the importance of determining pre-injury behaviour in order to exclude the possibility of symptoms being an exaggeration of pre-injury personality traits.[8] Additionally, psychosocial factors must be deduced to identify possible triggers.[2,7]

Clinicians must be aware that aggression can be a presenting feature of other psychiatric disorders. Depression has a prevalence of 18.5% to 61% in post-TBI patients and is linked with aggression due to their shared association with frontal lobe lesions and serotonin level imbalance.[9] Other differentials include manic disorders (which can involve a more marked aggressive component if secondary to TBIs), anxiety disorders and alcohol and/or substance abuse. Personality and behavioural disorders such as affective lability, behavioural disinhibition and acquired antisocial behaviour should also be considered.[8]

Management guidelines

The National Institute for Health and Care Excellence (NICE) refers to the Scottish Intercollegiate Guidelines Network (SIGN) for rehabilitating patients with acquired brain injuries (ABIs). Psychological treatments advocated by SIGN include CBT, contingency management procedures, music therapy and comprehensive neurobehavioural rehabilitation (CNR).[10] Family involvement appears to be associated with better outcomes[2] and is also recommended.[10]

Of the studies quoted by SIGN, CNR was found to cause a positive effect in ABI patients in one systematic review although inconsistent results were obtained for the other three methods. Regarding pharmacological treatment, SIGN advises propranolol and pindolol as first line options.[10]

Table 1: Overview of candidate pharmacological options for aggression

Cause of aggression	Candidate pharmacological options
Impaired behavioural regulation	Antidepressants
	Antipsychotics
	Beta blockers
	Methylphenidate
	Amantadine
	Buspirone
Hyperactive limbic drive	Anticonvulsants
	Benzodiazepines

Pharmacological treatment

The aberrant neurotransmitter changes in the cortex and limbic areas as a result of TBIs[2] provide targets for pharmacological therapy (as summarised in Table 1). Theoretically, cortical behavioural regulation can be enhanced by serotonergic agents and antagonists of dopaminergic and noradrenergic neurotransmission. Limbic hyperactivity can be dampened by the use of gamma aminobutyric acid (GABA) agonists, glutamatergic antagonists and anticholinergics.[6]

Impaired behavioural regulation

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) are indicated for their increase in dopamine and serotonin availability and the treatment of depression contributing to aggressive behaviour. In a trial conducted by Kant et al (1998), sertraline reduced aggression within one week of treatment although TBI severities were variable within the population.[11] These results are mirrored in other trials presenting sertraline as a viable treatment option.[12] Citalopram used in conjunction with carbamazepine successfully treated behavioural symptoms in a clinical trial of 22 patients conducted by Perino et al (2001)[13] although the separate effects of both drugs are impossible to differentiate. A case study by Sloan et al (1992) found that fluoxetine improved emotional lability in one patient within a week.[13]

Tricyclic antidepressants have been shown to be useful for managing both post-traumatic and chronic aggression. Amitriptyline has reduced aggression with good tolerability despite its strong anticholinergic side effects in several studies and is suggested as the best option for treating behavioural disorders secondary to frontal lobe injuries without impairing cognition.[13]

Antipsychotics

There is a wide body of literature advocating antipsychotics for managing aggression due to their sedative effects.[13] Nevertheless, the cognitive and extrapyramidal side effects of typical antipsychotics limit their value for chronic use. Comparatively, atypical antipsychotics have a milder side effect profile and are preferred although their cognitive impact in TBI patients is unclear.[2] Furthermore, unlike older generations, atypical antipsychotics antagonise 5HT2 receptors and are therefore implicated in reduced aggression.[5]

Of the typical antipsychotics, chlorpromazine reduced explosiveness in one case study conducted by Sandel et al (1993). Various case studies also report haloperidol improving chronic agitation in TBI patients although significant side effects were encountered.[13] Of the atypical antipsychotics the level of evidence is low. Quetiapine reduced aggression and irritability in seven patients in a trial conducted by Kim and Bijlani (2006).[11] Olanzapine significantly reduced aggression within six months in a case study conducted by Umansky and Geller (2000). Clozapine was associated with varying levels of improvement in six case studies conducted by Michals et al (1993) however seizures were experienced in two patients.[13]

Overall, there is no reliable evidence advocating antipsychotic use for managing chronic post-TBI aggression. If antipsychotics are commenced for this purpose, it is suggested that their use is restricted to patients with psychosis.[13]

Beta blockers

Beta blockers are useful for cases where aggression is caused by underlying anxiety[13] due to its inhibition of noradrenergic levels.[9] A Cochrane review of four RCTs found that pindolol and propranolol reduced aggression within two to six weeks of starting treatment in ABI patients however no recommendations were made due to heterogeneity between samples, a small number of trials and small sample sizes. The authors acknowledge that the trials involved high doses and so recommend caution when prescribing beta blockers for aggression.[4]

Methylphenidate

Methylphenidate is a psychostimulant indicated for its enhancement of dopamine and noradrenaline in the frontal lobe improving arousal and alertness.[13] Mooney (1993) found in a single RCT that methylphenidate significantly improved anger scores in TBI patients.[4] However other studies have yielded mixed results[12,13] and no firm conclusion can be made.

Amantadine

Amantadine increases dopamine availability and acts on glutamatergic pathways. An advantage of its use is its non-sedating qualities however there is contradicting evidence for its efficacy.[13] An RCT conducted by Schneider (1999) found no significant improvement[4] however the trial was limited by a small sample size and large heterogeneity. Interestingly, studies of a lower level of evidence demonstrate favourable results.[13] Due to this variability, its efficacy is still in question.

Buspirone

Buspirone – a serotonergic agonist licensed for treating anxiety[13] – has also reduced aggression in several case studies[2,12,14] warranting further research. Its side effects are amenable for use in TBIs although one disadvantage is its delayed onset.[13]

Hyperactive limbic drive

Anticonvulsants

The mood stabilising effects of anticonvulsants are mediated through their enhancement of GABA transmission.[2] Carbamazepine has been demonstrated in studies to be effective for managing acute and chronic post- TBI aggression.[12,13] Its side effects include impaired balance, sedation[13] and cognitive impairment particularly in brain injured patients[2] due to their heightened sensitivity. In a trial conducted by Mattes (2005), Oxcarbazepine reduced impulsive aggression however the number of TBI participants in the sample was unclear. Nine of the 48 participants also dropped out due to adverse effects[11] suggesting more research is needed into its tolerability in TBI patients. Valproate has also been demonstrated to effectively manage behavioural and affective disorders[13] with a milder cognitive impact compared to carbamazepine.[2] Regarding other anticonvulsants, the evidence is of a lower standard. Pachet et al (2003) found that lamotrigine reduced aggression with good tolerability in one case study.[11] Topiramate has been demonstrated to effectively treat manic symptoms but due to its side effects of psychosis and cognitive impairment,[2] may be inappropriate for TBI patients. Case reports reference lithium to reduce post – TBI agitation however it may be unsuitable as a first line option due to its neurotoxicity.[13]

Benzodiazepines

Benzodiazepines are indicated for their anticonvulsive, anti-anxiety and sedative qualities facilitated by stimulation of the GABA receptor.[13] There is limited literature on their chronic use in TBI patients due to their side effects of agitation, cognitive impairment and tolerance[2] thus they are recommended to be more appropriate for cases of acute agitation or anxiety.[11]

Conclusion

There are many challenges in assessing and managing chronic aggression due to its complex aetiology. Previous literature presents

a selection of pharmacological options however, their effect on TBI patients has not been confirmed resulting in limited guidance. The heterogeneity between samples also renders it impossible to predict treatment outcomes in the TBI population warranting the need for low doses, slow titration and frequent monitoring.[13] A six-week trial period is advised by Fleminger et al (2006) to ascertain effects of treatment before trialling a new medication.[4] Patient and family education regarding realistic treatment outcomes and side effects of treatments is also necessary to ensure treatment compliance.[2] In future, a clarification of the underlying neurochemical changes is needed to identify further treatment targets. Additional larger scale RCTs are also needed to guide decision making and predict treatment outcomes. Table 2 offers a practical guide on medication choice in relation to aggressive behaviour in ABI.

Table 2: Medication choice of candidate pharmacological interventions; suggested practical guide

Predominant Presentation	Suggested drug / group
Depressive symptoms	SSRI
Episodic dyscontrol / 'mood swings'	Mood stabilisers / atypical antipsychotics
Paranoid behaviour	Atypical antipsychotics
Anxiety	SSRI / Buspirone / B-blockers

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Neurological literature: a clinical trial

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Clinical trials are an integral part of neurology. Many neurologists will have been involved in their conduct, and all will apply their outcomes to clinical practice. A working knowledge of the methodology of clinical trials is fundamental to their evaluation, and hence a learning objective for neurological trainees.

Sinclair Lewis (1885-1951) was the first American winner of the Nobel Prize for Literature, in 1930, following a series of acclaimed novels published in the 1920s. In one of these, *Arrowsmith* (1925), the protagonist, Martin Arrowsmith, is a doctor (as was Sinclair Lewis's father), whose medical career the novel charts, from medical student, to country doctor, to public health official, to research scientist.[1] In the latter context, a description of a clinical trial is to be found.

Narrative

Aged 34 (p. 322), and hence, from internal evidence, in about 1917, Martin discovers "the X Principle" which destroys staphylococcus, but the novelty of his finding is short-lived as his scientist mentor Max Gottlieb finds a report from D'Herelle of the same phenomena, described as bacteriophage (p. 327). Martin's subsequent researches focus on the possibility of curing bubonic plague with phage (p. 337). Aged 37 (p. 384), and hence around 1920, the opportunity arises to put this laboratory discovery into clinical practice.

The scene is the fictional Caribbean island of St Hubert, a "British possession" (p. 355) located in the Lesser Antilles (pp. 352,355) between Barbados and Trinidad (p. 343) where there is an epidemic outbreak of bubonic plague (p. 348). The plan of Max Gottlieb is "to use the phage with only half [of the] patients and keep the others as controls, under normal hygienic conditions but without the phage" (p. 348), thus permitting "an absolute determination of its value" (p. 348). On departure, he urges Martin: "do not let ... your own good kind heart, spoil your experiment" (p. 354).

Martin's co-worker on the trip, Gustaf Sondelius, wants to give phage to everybody (pp. 349,381) since "in this crisis mere experimentation was heartless" (p. 350) and on principle twice refuses treatment for himself (pp. 352,378), but Martin insists on having "real test cases" (p. 349), perhaps a reflection of his training from Gottlieb as a medical student in the importance of controls (p. 40). Martin's final plan: in "a district which was comparatively untouched by the plague ... one half injected with phage, one half untreated. In the badly afflicted districts, he might give the phage to everyone, and if the disease slackened unusually, that would be a secondary proof" (p. 350).

On St Hubert, both the Governor of the island (pp. 375-6) and the Board of Health (p. 377) object to the plan of "half to get the phage, half to be sternly deprived" (p. 375) despite Martin's assertion that the "luckless half would receive as much care as at present" (p. 377).

In the village of Carib, where "every third man was down with plague", Martin "gave phage to the entire village" (p. 379), following which there is an apparent slackening of the epidemic in the village, observations which Martin hopes will prompt the local bureaucracy to "let me try test conditions" (p. 379). Carib village is then burnt in order to kill all the rats, the locals evacuated to a tent village where Martin remains for two days giving them phage (p. 380).

The opportunity for experiment is provided in St Swithin's Parish, where, unlike Carib, "the plague had only begun to invade" (p. 386). Martin "divided the population into two equal parts. One of them ... was injected with plague phage, the other half was left without" (p. 386). "The pest attacked the unphaged half of the parish much more heavily than those who had been treated ... These unfortunate cases he treated, giving the phage to alternate cases" (pp. 386-7).

However, following a personal bereavement, Martin damns experimentation and "gave the phage to everyone who asked" other than in St Swithin's parish where "his experiment was so excellently begun ... some remnant of honor [kept] him from distributing the phage universally" (p. 392). Unsurprisingly people from St Swithin's are seen in the queue for treatment in the main town of St Hubert, Blackwater (p. 393). Eventually Martin "went back to the most rigid observation of his experiment in St Swithin's ... blotted as it now was by the unphaged portion of the parish going in to Blackwater to receive the phage" (p. 394).

Six months after Martin's arrival, the "plague had almost vanished" (p. 395). Martin is lionised by the populace as "the saviour of all our lives" but one local doctor reflects that "plagues have been known to slacken without phage" (p. 396). Martin knows that he does "not have complete proof of the value of the phage" (p. 397), that "his experiment had so many loopholes" (p. 400). He plans to take his data to a "biometrician" who may, he notes, "rip 'em up. Good! What's left, I'll publish" (p. 400). Raymond Pearl, the biometrician, "pointed out that his agreeable results in first phaging the whole of Carib village must be questioned, because it was possible that when he began,

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the curve of the disease had already passed its peak" (p. 404). It is evident to Martin's friend, Terry Wickett, that "you bunged it up badly" (p. 405).

Comment

Arrowsmith has previously attracted attention for its portrayal of contemporary immunology[2] and public health,[3] and belatedly I discovered a prior commentary related specifically to the details of the clinical trial.[4] Whilst literary accounts of neurological illness are often to be found, I have not previously encountered a fictional account of a clinical trial.

It is not difficult to enumerate the many shortcomings in this clinical trial: no ethics, no planning, no involvement of a statistician from the outset, no patient consent, no blinding of any kind, no randomisation, no matching of cases and controls, no clear definition of outcomes, etc. Indeed this might be better termed a "therapeutic experiment" rather than a clinical trial. Of course, there is no reason why Lewis as author should present the perfect trial, motivated as he was by literary rather than scientific concerns, specifically to illustrate the tension between Martin as clinician-scientist and clinician-humanitarian.[3] Although the randomised clinical trial as we know it was not to evolve for several more decades, clinical trials characterised by "fair allocation" schedules had been undertaken at least from the time of James Lind.[6]

Sinclair Lewis was awarded the Pulitzer Prize for fiction for *Arrowsmith*, but he declined it, his previous novels (*Main Street*, *Babbitt*) having been passed over. In the same year, 1926, the surgeon Harvey Cushing (1869-1939) also won a Pulitzer Prize for his biography of Sir William Osler (1849-1919). According to another Osler biographer, Michael Bliss, "Cushing wrote friends that he had nothing but contempt for the spirit of Lewis's novel, which had mythologised research and denigrated medical practice. Cushing hoped his Osler biography would be an antidote to *Arrowsmith*".[7] Cushing's objection may have been to the "Literary stereotypes that portrayed surgeons as money-grubbers in novels of the early 20th century":[8] his name appears in the novel (p. 85) in a list of surgeons with exceptional surgical technique. He may also perhaps have baulked at a description of one of Martin Arrowsmith's medical student chums "reading a Sherlock Holmes story which rested on the powerful volume of Osler's Medicine which he considered himself to be reading" (p. 61; although Holmes' creator was, of course, medically qualified and the Holmes oeuvre features some interesting medical material[9]). Osler is mentioned elsewhere in *Arrowsmith*: as the "god" (p. 82) of the professor of internal medicine and Dean of Arrowsmith's medical school who is a "fit disciple of Osler" (p. 127), and his treatment of diphtheria is cited (p. 158). Lewis had been "fed inside knowledge"[10] for the novel by the microbiologist Paul de Kruif (1890-1971), later to gain fame with his book *The Microbe Hunters* (1926),[11] who is acknowledged at the start of the novel.

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Brush with Greatness

The year was 1994, and I had just completed my stint in research in Creutzfeldt-Jakob disease (CJD) with Bob Will, at the National Surveillance Unit in Edinburgh. Some of the work I had done with the team had been accepted for presentation at a joint ABN/ANA conference in San Francisco. I set off proudly, clutching two posters, accompanied by one of the Neuropathologists from the unit – James Ironside. San Francisco was of course the base of Stanley Prusiner, who had proposed the "prion" hypothesis, as the explanation for some of the unique aspects of the spongiform encephalopathies. At the time the theory was still under scrutiny and the subject of much debate (although a few years later Prusiner was partially vindicated by the award of the Nobel prize in Medicine; the same mechanism is now thought to underlie many more (possibly all?) degenerative disorders affecting the brain associated with abnormal proteins, including (perhaps) Parkinson's disease). It seemed appropriate that James and I should visit Prusiner in his laboratory, during our visit. It smacked a little of paying homage, but we were excited by the prospect of meeting this controversial character, and it was simply too good an opportunity to miss.

The conference passed without event, and my posters were accorded the appropriate lack of interest they deserved. Undeterred, James and I set off for Parnassus Heights one October morning, to the UCSF campus there. Prusiner breezed in, a few minutes late, but was polite, genial and duly condescending. We had gone armed with more data from the unit. Variant CJD had not yet appeared, but James, Bob and others were already engaged in an intensive (and ultimately rewarding) surveillance exercise. We showed Prusiner the data we had been collecting, and he listened patiently to us, rather like a kind Montessori teacher. His time was clearly precious, and after half an hour, he indicated that our time was up by looking at his watch very deliberately.

We hastily concluded our chat, and got ready to leave. Prusiner, perhaps feeling a little sorry for us by then, started asking what we planned to do the rest of the day. The conference organisers had arranged various excursions after the meeting, one of which was a walking tour of San Francisco's fabled Chinatown. Our meeting with

this famous scientist took a surreal turn at this point, when I explained that I was hoping to join this tour that afternoon. Prusiner reposted by asking what time I needed to be at the airport. I looked at him curiously, but also with some bewilderment. Did he not know that there was a Chinatown in his own City, and that you didn't need to fly to get there? Was he really the great man...and, crucially, should he be a Nobel prize contender? It dawned on me that he had not understood my British-Sri Lankan accent, and thought that I was going to visit China! More explanations followed, and we departed, flushing.

Prusiner did receive the Nobel prize in 1997, and many more accolades followed. Our meeting with him took place at a heady time: the world was fascinated by these disorders and the potential impact of Bovine Spongiform Encephalopathy on humans. Neuroscientists too were intrigued by "prion" biology, and the extent to which Prusiner's theory accounted for our clinical and laboratory observations. It was a privilege meeting him, seemingly at the height of his career, that day, although from his perspective it was a considerably more pedestrian encounter, I suspect. However puerile, what made the memory of that meeting indelible for me was a rather embarrassing misunderstanding – one which did make me query, however briefly, his brilliance!

An expert opinion: upper limb rehabilitation after stroke

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Key take home messages

1. Clinically meaningful improvements are possible in chronic stroke patients
2. The dose of rehabilitation treatment needs to be larger than currently delivered
3. Rehabilitation is a complex intervention that cannot be reduced to a single element

Somewhere between 50-80% of stroke survivors have upper limb symptoms after acute stroke[1] and persistent difficulty in using the upper limb is a major contributor to ongoing physical disability.[2] A commonly held view is that most recovery from stroke occurs over the first three to six months after which little improvement is possible, especially at the level of impairment.[3-6] We argue that this may be a self-fulfilling prophecy resulting in lack of provision of potentially helpful rehabilitation.

What is the best way to promote upper limb recovery after stroke? Most studies of behavioural interventions have investigated forms of constraint induced movement therapy (CIMT),[7,8] repetitive task training (RTT)[9] or robotics,[10] each of which focuses on increasing the activity of the affected limb. Kwakkel et al[8] suggested that motor function, arm-hand activities and self-reported arm-hand functioning in daily life, improved immediately after CIMT and at long-term follow-up, but the comparison was often with usual care. It is worth noting that CIMT approaches were said to be more likely to be successful in promoting long term benefits if the protocol included shaping, massed practice and a behavioural transfer package, whereas simple forced use therapy was ineffective.[8] RTT also has some evidence to support benefits over what is described as usual care, but the evidence for benefits over 'matched therapy' is less strong.[9] The use of robotics can increase the number of movement repetitions, but has failed to produce clinically meaningful effects.[10] Indeed, the recent RATULS study showed that compared with usual care, approximately 23 hours of robot-assisted training and matched dose 'upper limb therapy' did not improve upper limb function.[11] Overall, it would appear that asking patients to make simple repetitions of movement, however meaningful the task, is relatively ineffective without some way of actively translating any improvements into activities of daily living. Simply increasing the number of repetitions does not appear to be effective,[12] and this in itself should give us pause for thought.

A few studies have tested more complex therapies incorporating a number of different elements. The ICARE study[13] of upper limb treatment after stroke went beyond simple repetitions, using a structured, task-oriented motor training programme that was impairment focused, task specific, intense, engaging, collaborative, self-directed, and patient centred, starting about six weeks post-stroke. Outcomes were not improved by this approach, but on reflection it is likely that, as with many of the studies, the dose of 30 hours over ten weeks was too low (the usual care group received 11.2 hours over ten weeks). Despite scepticism that stroke patients would be able to 'tolerate' much higher doses,[12] one study managed to deliver 300 hours of upper limb therapy to chronic stroke patients over twelve weeks and reported changes in measures of both impairment and activity that were far greater than those in lower dose studies,[14] and in fact the findings of this study have recently been replicated by the same group.[15] We recently reported the findings of the Queen Square Upper Limb (QSUL) Neurorehabilitation programme,[16] a single centre clinical service that provides 90 hours of treatment focusing on the post-stroke upper limb. Most patients entering the programme were in the chronic stage (> 6 months post-stroke), but were able to complete the 90 hours of the programme, even though they exhibited a wide range of impairments and fatigue levels. Despite the time since stroke (median = 18 months) we observed (i) large clinically meaningful improvements in upper limb impairment and activity (of a magnitude similar to those reported by McCabe et al.), and importantly (ii) that these changes were maintained, or even improved upon, six months after treatment.

The first lesson to take from these studies is that post-stroke rehabilitation programmes and clinical trials are almost certainly under dosing patients. In future, clinical trials must investigate the effects of much higher doses

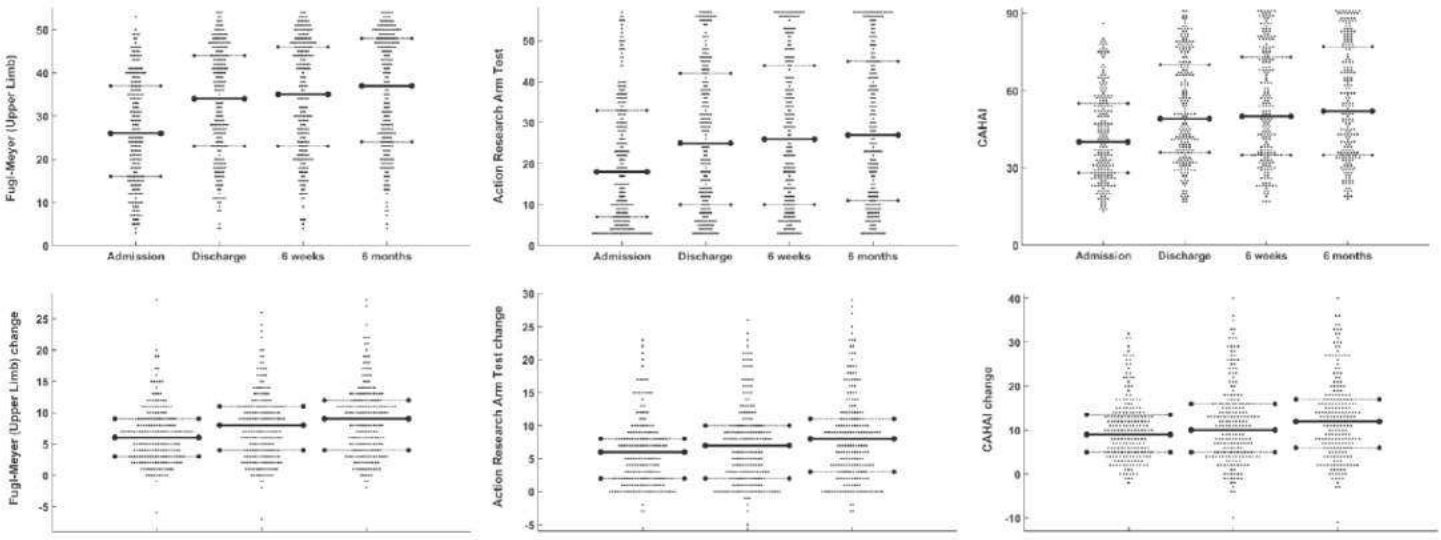

Figure 1. Outcome scores for all patients on the Queen Square Upper Limb Rehabilitation programme. Each data point represents a single patient. Top row shows individual scores at admission, discharge, six weeks and six months after discharge. Bottom row shows the individual difference scores for admission to discharge, admission to six weeks post-discharge, and admission to six months post-discharge. Scores are shown for modified Fugl-Meyer (upper limb), Action Research Arm Test and Chedoke Arm and Hand Activity Inventory (CAHAI). Median (solid line) and upper and lower quartiles (dotted lines) are shown. (Reproduced with permission from Ward et al. J Neurol Neurosurg Psychiatry. 2019 May;90(5):498-506).

than are currently being used. The second question to be raised is what are the key 'active ingredients' of an upper limb rehabilitation treatment? Whilst it is not clear what the optimal behavioural approach for promoting upper limb recovery should be, it is clear that simple protocol driven approaches have not led to large or sustained effects,[17] both of which are necessary to produce a step change in stroke recovery. Successful post-stroke neurorehabilitation is likely to require a combination of complimentary approaches. If we accept this premise, then we are unlikely to determine the optimal combination of active ingredients simply by studying each approach in isolation, because the interactions between these elements will also have to be considered.

So how do we work out what the 'active ingredients' of upper limb rehabilitation are? A more sensible way forward is to look at interventions that have already demonstrated a high level of efficacy and then begin to work out their key components. Here, it is important to say that we need to start with treatments that have a high chance of achieving minimum clinically important differences (MCID) rather than small changes that might be statistically significant. Both McCabe et al[14] and Daly et al,[15] as well as the QSUL programme,[16] produced large improvements on both impairment and activity limitation and both involved more complex treatment approaches, not restricted to one element. It is worth considering these in more detail.

- Analysis of movement and performance in activities of daily living. The initial assessment is crucial. The question, 'why does this person's hand and arm not work' should never be answered with 'because they have had a stroke'. There needs to be an appreciation of the range of potential contributory impairments (patterns of weakness, spasticity, loss of joint range, shoulder restriction and pain, sensory loss, apraxia, cognitive deficits, depression, apathy, fatigue etc.) because each of these becomes a therapeutic target. Our view is that without informed clinical reasoning based on the presence or absence of specific impairments, the correct treatment approach is unlikely to be selected.
- Identify and treat barriers. Avoid complications that will prevent participation in an active rehabilitation programme. We commonly see loss of passive joint range preventing people accessing finger or thumb movement, due to either spasticity or non-neural shortening. This can happen at most joints, but particularly in the hand. As well as increased finger flexion, be alert to loss of flexion at MCP joints which makes it difficult to shape the hand properly. Treatment involves splinting and optimal spasticity management. We also see pain and restriction of range in the shoulder. Restriction of external rotation in particular should raise the possibility of adhesive capsulitis. Despite the lack of a clear evidence base for treating post-stroke adhesive capsulitis, anecdotally we have had success with capsular hydrodilatation followed by physiotherapy.
- Preparation. Manual techniques are used to optimise and improve baseline at an impairment level, for example mobilising joints to improve range, lengthening and strengthening muscles to ensure they are at a biomechanical advantage to generate force, training sensory discrimination and improving postural control and balance.
- Reduction of impairment and re-education of quality and control of movement within activities of daily living. Individualised meaningful tasks are practiced repeatedly in order to facilitate task mastery with a focus on quality of movement. This is achieved through (i) adaptation of the task, e.g. decomposing tasks into individual components to be practiced; (ii) adaptation of the environment, e.g. fabrication of functional splints and adaptation of tools such as cutlery or screwdrivers, to enable integration of the affected hand in meaningful activities; (iii) assistance, e.g. de-weighting the arm to allow strengthening and training of movement quality and control through increased range.
- Coaching (involving instruction, supervision, reinforcement) was considered a key component of the QSUL programme, used throughout to embed new skills and knowledge into individual daily routines. Consequently, individuals increase participation and confidence in their desired goals, enhancing self-efficacy and motivation to sustain behavioural change beyond the end of the active treatment period.
- Sustaining change. Our view is that the approach described, delivered at a high dose is most likely to achieve clinically meaningful improvement together with improved self-efficacy and behaviour change that results in retention of gains or further improvement (something not routinely seen with many upper limb interventions that have been investigated).

Rehabilitation is often criticised for not following standardised approaches that lend themselves to investigation through clinical trials. However, when single elements are then studied in isolation the results are often not clinically meaningful and are not sustained.[18,19] Looking at the difference between these approaches and those taken by McCabe et al[14], Daly et al[15] and QSUL[16] should be informative, with a view to formally describing the key elements of a successful treatment. Whilst approaches at the activity and participation level will vary as they are tailored to an individual's specific meaningful goals, the overall therapeutic approach taken towards specific

impairments should be the same across all patients. Ideally, it should be possible to describe the principles of an optimal intervention using a format such as the TIDIER guidelines.[18,19]

There is a way to go before we can really say we understand both the treatment itself and the effects of the treatment on individuals. This will require careful assessment of both the 'input' (the nature of the behavioural intervention) and of the 'output' (the resulting behavioural change) at a level of fine-grained detail that is not currently achieved on a regular basis, for example using kinematic[20] or neurophysiological[21] assessment. In addition, this input-output relationship will be modulated by a number of patient characteristics, which could relate to behavioural characteristics (e.g. severity, presence of multiple impairments) or to biological characteristics (e.g. the nature and extent of brain damage, time since stroke, age, medication).

Overall, our experience suggests that much higher doses and intensity of upper limb neurorehabilitation can be delivered with beneficial effects. We have highlighted the need to consider the dose and the nature of the intervention as well as appropriate patient stratification in informing future clinical trial design.

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The Myotonic (Holmes Adie) pupil

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The harmless condition of a dilated pupil which reacts abnormally slowly (myotonic) to light and convergence was fully described in 1931 by William John Adie (1886 – 1935),[1] of the National Hospital, Queen Square:

> I wish to draw attention to a benign symptomless disorder characterised by pupils which react on accommodation but not to light, and by absent tendon reflexes. Five of the six cases I am about to describe came under my notice in the course of a few weeks;... Though harmless in itself it merits recognition because it is often mistaken for a manifestation of syphilis of the nervous system, with unfortunate consequences... Mr Foster Moore has described seven cases under the title 'Non-luetic Argyll Robertson pupil.[2]

Usually seen in females, in 80% cases it is unilateral. Adie was not the first to observe this uncommon curiosity and its variant manifestations. In 1818 the London ophthalmologist, James Ware (1756–1815), described a patient who may have had a myotonic pupil.[3] His patient, whose pupillary abnormality had been known for twenty years, was:

> A lady between thirty and forty years of age, the pupil of whose right eye, when she is not engaged in reading, or in working with her needle, is always dilated very nearly to the rim of the cornea; but whenever she looks at a small object, nine inches from the eye, it contracts, within less than a minute, to a size nearly as small as the head of a pin. Her left pupil is not affected like the right; but in every degree of light and distance, it is contracted rather more than is usual in other persons.... Several instances have come under my notice, in which the pupil of one eye has become dilated to a great degree, and has been incapable of contracting on an increase of light,

Figure 1. WJ Adie from: Alastair Compston: Idiopathic narcolepsy: a disease sui generis: with remarks on the mechanisms of sleep. By WJ Adie. Brain, 2008;131:2532–2535. https://academic.oup.com/brain/article/131/10/2532/1746741.

Adie stated: 'The tonic or myotonic pupillary reaction was first described in 1902 by Saenger in the left pupil of a 34 year old woman)[4] and by Strasburger in a 17 year old man[5] independently.[6] Later in the same year both Saenger and Nonne reported further cases for which Saenger proposed the name 'myotonic pupillary movement' to distinguish it from other forms of mydriasis or abnormal pupillary reflexes. Later, Adie related 'atypical' forms, less clearly defined, but he included some forms of 'internal ophthalmoplegia and complete light rigidity with atonic convergence reaction.'

Before Adie, Hughlings Jackson in 1881 had also clearly described the same disorder:[7]

> A woman aged 26 was sent to see me simply because the right pupil was much larger than the left. It had been so three years...the right pupil was dilated and absolutely motionless to light, and also during accommodation, yet the accommodation itself on this side was perfect; this was severely tested by Mr Couper... this case at first puzzled me...It occurred to me to test the knees. Neither I nor Mr Couper found the smallest trace of the knee phenomenon [knee jerk]. Several times did I pertinaciously inquire for other symptoms of tabes; there were no other symptoms of any kind....Dr Buzzard ... confirmed the above observations.[8]

In 1906 Markus had described an isolated case of partial iridoplegia,[9] and Weill and Reys[10] also described a tonic pupil reactions to convergence and accommodation with areflexia. Some reports bear their names as eponyms.

Adie's more detailed, classic paper in 1932,[11] described 22 patients, with absent tendon reflexes, and noted 44 reported cases of tonic pupil in nine of which there were absent tendon reflexes. In this account he outlined four incomplete forms (the last would not now be accepted):

1. The complete form—typical tonic pupil and absence of reflexes.
2. Incomplete forms: a) tonic pupil alone; b) atypical phase of the tonic pupil alone (iridoplegia; internal opthalmoplegia); c) atypical phases of the tonic pupil with absent reflexes; d) absent reflexes alone.

At about the same time, Gordon Holmes found 19 patients with the myotonic pupils, characterised in his *Introduction to Clinical Neurology*:

> By very slow contraction on convergence, and even slower relaxation. The reflex to light is often lost too. One or both eyes may be affected.

Holmes's 1931 paper described it and its association with symptoms of other diseases of the nervous system:

> Frequently no change in the size of the pupil was visible immediately on convergence, but when this was maintained for a few seconds the pupil slowly and gradually grew smaller, till its diameter equalled or was even narrower than that of the normal eye. The rate of contraction varied very much...When contracted the pupil remains constant and when convergence is relaxed it dilates slowly... In the present state of our knowledge a separation of those cases in which the tendon jerks are absent from those in which they persist is unjustifiable . . . the similarity of the symptoms in all these cases naturally suggests a common aetiology.[12]

Edwin Bramwell linked Holmes's name with Adie's in 1936.[13] The brilliant George Bruyn mischievously pointed to the 'peculiarity' that Morgan, Symonds, Holmes and Adie all published at about the same time, in different journals without referring to each other, yet they knew each other well at Queen Square.[1] However Adie's second paper (1932) did mention Holmes's work.[11]

The credit must be Adie's for stressing its harmless nature and crucially by distinguishing it from neurosyphilis. Adie did not claim originality, recognising several earlier accounts. He acknowledged that Morgan and Symonds had recorded:

> In Guy's Hospital Reports for 1927 Dr. Symonds and I drew attention to a small

> group of cases in which certain abnormalities of the pupil, including inequality and defective reaction to light and convergence, and also some affection of accommodation, were associated with a pathological absence or diminution of the tendon- jerks.[14]

It was previously confused with the Argyll Robertson pupil associated with luetic tabes dorsalis or General Paralysis of the Insane, characterised by: a loss of both direct and consensual light reflexes; pupillary inequality; irregularity and iris atrophy without reaction to light. Adie clearly distinguished this from his myotonic (Pseudo-Argyll Robertson) pupil.

Since Adie's descriptions,[2,6,11] this conception of an atypical tonic pupil has been widened,[15] which unnecessarily complicates a diagnosis which is secure if clinical observations are precisely observed.

Pathogenesis

Stanley Graveson (1915-1976) studied 15 patients, three men, 12 women, aged 12 to 55.[16] He set out to illuminate: (1) the site of the anatomical lesion and (2) the nature and specificity, or otherwise, of the underlying pathological process. Two types of tonic pupil were distinguished, (a) the fixed type, and (b) the ordinary type of tonic pupil. The only common features of this latter variety are (1) their regularity of shape or position of the pupil and (2) the slowness of pupillary dilatation after convergence. Graveson pointed out that the lesion had to be on the efferent limb of the light reflex arc, to account for the absence of a light response in a unilateral tonic pupil with a simultaneous brisk consensual response in the normal pupil. The prompt reaction of the pupil to pilocarpine meant that the muscle of the iris could not be at fault.

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Scrabble-ing with dementia

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Introduction

In a previous article, it was suggested that board games, puzzles, and quizzes might be characterised as neuropsychological tests, probing different domains of cognitive function.[1] One of the board games mentioned, Scrabble, was deemed to tap essentially linguistic skills. In recent years I have had the opportunity to witness first-hand the changes in Scrabble skills in a previously competent player who developed dementia, namely my mother.

The game

For those unfamiliar with the game, the aim of Scrabble (originally marketed as "Criss-Crosswords") is to make words using one hundred letter tiles on a 15x15 board. Individual letters are assigned different values according to the frequency of their use (e.g. in the English version a, e, i, o and u all score 1, whereas q and z score 10). Each player has a hand of seven tiles, picked at random, with which to construct words, which may run either horizontally or vertically on the board, building upon letters already in place on the board. Scores for each turn are the sum of the individual letter scores, and these may be augmented by placing tiles on squares labelled as double or triple letter or double or triple word scores. The player with the highest aggregate score once all the letters are played wins the game. For those unfamiliar and/or curious, the full rules may be consulted.[2]

Although purchased initially for the entertainment of their children, my mother and father continued to play Scrabble frequently, often nightly, after we had passed on to other interests, and indeed after we had left home.

The patient

My mother developed cognitive decline in her mid-eighties, having previously been in good health aside from occasional migraine (with perimenopausal onset[3]) and late life hypertension. An elective hip replacement in her eighties was certainly associated with change in cognitive and functional abilities. She was diagnosed with Alzheimer's disease in her early nineties, based on clinical assessment and cognitive testing (ACE-III 49/100) by an old age psychiatrist. She is treated with donepezil. My sister is her named carer and provides resident assistance for all activities of daily living.

Now 94, my mother continues to play Scrabble on a daily basis. Although she never initiates the plan to play, she generally expresses willingness if it is suggested, often commenting that it keeps the mind active and provides an opportunity to learn new words. She perseveres at each game, never expressing any wish to stop playing once a game is underway, although on occasion a game has been terminated because she is in pain (particularly from the previous hip replacement).

Observed changes in Scrabble skills

My mother is sometimes slow in making words, and certainly her playing vocabulary is impoverished in comparison with her past abilities, now with a predilection for short (usually three- or four letter) words. Nevertheless, she can on occasion "see" words and play immediately (pre-processing?), such that usual turn taking may be overridden in her enthusiasm to play a word, requiring a reminder that "It's not your go yet!". When it is her go, the previously formulated word may have been forgotten.

Difficult letters, such as q, z, and j, may be marginalised, literally and physically, and apparently ignored, sometimes for the whole duration of a game. The two blank tiles, which can be used to represent any letter, are often a source of confusion, and may be turned upside down. Nevertheless, she can sometimes surprise us by working out unfamiliar words (e.g. from an opening hand of letters, d,d,e,j,r,s,u, she eventually played all seven as "judders").

On occasion she may play letters in the wrong direction (i.e. backwards), suggesting visuospatial problems, or may attempt to play a word for which she does not have all the letters. She may make a word with the tiles in her hand which cannot be played onto the board for lack of a suitable letter/space to which it can be joined.

Playing strategy has also changed in other ways. Whereas in earlier years the opportunity to play on, for example, a triple word score would not be overlooked, this is no longer the case. She does not calculate or keep her own score. Generally her completed game scores are between 100-150, occasionally 200, whereas in her heyday she regularly scored around 300.

The option to replace some or all of a hand of letters in exchange for foregoing a turn of play, which she frequently used in the past if stuck with a handful of vowels, is never now used. The use of a dictionary to check word spelling is eschewed, indeed those availing themselves of this facility, entirely within the rules of the game, may be accused of cheating!

In summary, I suggest that my mother's current standard of Scrabble play reflects a general decline in her linguistic skills, perhaps some loss of memory for words, occasional visuospatial errors, and change in executive function as reflected in her less competitive strategy.

Another phenomenon, which seems very curious, occurs on occasion. Despite her experience of playing Scrabble over many decades, my mother will sometimes state "I don't think I've played this game before". With encouragement and example she may pick it up again, but on other occasions this is not the case. She may report that she just cannot see how she could play the letters in her hand, sometimes laying them on top of letters already on the board. I wonder if this is a form of "closing in", a term used to describe copying drawings close to or superimposed upon the original, seen in some patients with Alzheimer's disease, and variously interpreted as "constructional apraxia" or a visuospatial deficit. This fluctuation in the ability to play occurs particularly (but not invariably) in the afternoons, and I think might reflect waning of attentional resources, manifest as an executive deficit of not understanding how the game is played.

Conclusion

My previous judgment that Scrabble is essentially a test of linguistic skills[1] has been shown, in part from observation in the change in my mother's play, as far too simplistic. Evidently, Scrabble requires the allocation of attentional resources, intact verbal and visual memory, visuospatial skills, and executive function, as well as linguistic abilities, for its successful performance.

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The effect of machine learning and artificial intelligence on the use of robots in neurosurgery

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Abstract
Robotics has made rapid inroads into specialised fields of surgery like neurosurgery. The robot has many advantages like increasing accuracy, eliminating muscle fatigue and physiological tremor during long operations, all of which improve outcomes and avoid potential complications in high risk neurosurgery procedures. At present, we use pre-programmed robots to guide the surgeon accurately localising the brain anatomy. This allows the surgeon to place electrodes in the brain or pedicle screws in the spine or take precise biopsies. Use of robots in Neurosurgery are presently limited to these tasks. In future, robots will have to perform these tasks and other complex procedures without the involvement of the surgeon.

For this to happen, robots will need be equipped with algorithms and software to help them to learn without being programmed, that is, via machine learning. At the core of this process is the ability of the robots to exploit large amounts of data based on their computational power and then translate it to actions that would mimic the surgeon. Progress on this front has been slow, mainly due to ethical (data access) and safety issues. It is felt that with the ability of newer generation computers to absorb and analyse tremendous amounts of data (e.g. thousands of operations of a particular kind), machines will learn to copy the actions of the surgeon and make safe choices so they can be trusted to perform the surgery and manage any unforeseen events which may arise from the surgery.

The two main challenges that hinder complete automation are surgical perception and tissue manipulation. Neurosurgery operates within severe spatial constraints and the consequence of any tissue injury is likely to be catastrophic. The tactical nous and fine sense acquired by an experienced surgeon in his hands can be learned by the machine through the development of haptic feedback through tissue resistance. Long distance robotic surgery supervised by a distant surgeon (Telesurgery) can only be safe if used over a dedicated network. This will ensure telecommunication is uninterrupted during the procedure and information exchange is concurrent. The risk to safety increases significantly with latencies above 200ms and exponentially above 1000ms.

In this article, we discuss the current situation, the future possibilities and the factors which are an obstacle to the quick adoption of AI and ML in neurosurgery.

Machine learning in surgery, past, present and the future

The potential for machines and other artificial forms of intelligence such as robots to enhance the ability of the surgeon to perceive, act, and extend their capabilities beyond current limitations has been a major contributor to the ever-increasing presence of robotics in neurosurgery and surgery as a whole.[1] Nevertheless, the complete automation of the robots is a significant challenge, principally due to the problems associated with machine learning. Surgeons traditionally rely on their experience and expertise to perform operations; in contrast, robots and other artificial intelligence forms must be equipped with algorithms and software to help them to learn without being programmed, that is, via machine learning. At the core of the process is the ability of the robots to exploit data based on their computational power and translate it to actions that would mimic the typical surgical procedure performed by a human being, via the algorithms that make them equipped to postulate various problem-solving models.[2]

Globally, the last few decades have seen the invention, integration, and incorporation of various machines into the practice of neurosurgery. For example, common devices used in the last thirty years in neurosurgery include, the PUMA 200, NeuroMate, Pathfinder, Neuroarm, Spine assist, Renaissance, the Steady hand system, Neurolocate, iArms, EXPERT System, iSYS1 Robot, Spinal robotics, Augmented Reality systems, Neurosurgical lasers, the Da Vinci robot, SOCRATES and ROSA. Clinically, each robot has different applications in surgery. For example, the earliest robot, the PUMA 200, aids in performing of stereotactic surgery, where surgeons use CT guided biopsy needle to access tissues in the brain; Neuromate is a stereotactic system that is useful in doing various deep brain procedures such as stereo-encephalography, with six degrees of freedom and is considerably safer than the PUMA

200 for biopsies in surgery; Renaissance is a relatively newer image-guided system that is applicable in keyhole neurosurgery and uses an automated system that relies on MRI/CT scan images to insert needles, catheters, and drill the skull; The iArmS is equally a later invention that follows the movement of the surgeon. In operations, it prevents fatigue and trembling during microscopic procedures.[3] As a result, it is beneficial in long and time-consuming procedures which are typical of neurosurgery.

However, to date, no completely automated machines have been deployed in the field of neurosurgery. Instead, optimisation of present technology with an increased master-slave relationship between human and machines has dominated present integration of artificial intelligence into neurosurgery.[4] Nonetheless, it is critical to note that modern technology has allowed for the use of various miniaturised systems uniquely designed to serve specific elements in operations. The outcome evident with robots such as the neuroMate, SpineAssist, Renaissance, steady hand system, and Neurolocate indicate a bright future for machine learning and use in the field of neurosurgery.[3]

The current thought is that, although the industry will likely continue to experience a growth in adoption of robots in surgery, complete automation will not happen over the next two decades.[5] It is argued that, at present, two main challenges hinder complete automation that would allow patients to have surgeries in hospitals without any human interaction. They include perception and manipulation. More than any other field, neurosurgery operates within severe spatial constraints and the potential consequences for even minor deviations may be catastrophic. For full automation to be realised, machines would have to learn to analyse the digital data such as images about soft tissues and then act on it appropriately without the aid of a surgeon.[6] Accordingly, it is logical to expect that although machine learning will allow for greater inventions with more processing capacity and independence levels, the near future of artificial intelligence in neurosurgery will still include the participation of surgeons as either observers or active participants, or to rescue and limit brain injury when there has been an unforeseen event during surgery. An example of such a situation would be the ability to tackle unexpected injury to a blood vessel in the brain. The robot may cauterise the vessel and stop the bleeding. This however, may result in a stroke with profound neurological deficit or death for the patient. Where safety margins are low with potential serious consequences, the focus must be on prevention and safety.

Master-slave robot relationship (Telesurgery)

In this situation, the surgeon controls the robot. The introduction of the da Vinci surgical system marked a new generation of robots, especially since it had seven degrees of freedom and four arms, making it distinct from its predecessors. It revolutionised robotic surgery through a functional design improvement of previous machines.[7]

With modern development, the relationship between machines and surgeons has also progressed. Typically, robotics is classified either according to their level of autonomy or functional design. In this vein, robotic systems applicable in neurosurgery can be broadly categorised into three (handheld shared/controlled systems, the telesurgical, and the supervisory surgeon-controlled robot), according to the level and relationship between machines and the surgeons. For instance, telesurgery robots employ a master-slave relationship where the surgeon takes control of a surgery by controlling the robot's actions remotely. The NeuroArm is one of the most applied tele-surgical robots and was developed in 2001 as a refined master-slave system to aid in neurosurgery, which allows surgeons to perform microsurgical and stereotactic procedures using data collected from real-time MRI and is structurally designed to withstand strong magnetic fields of MRI without altering the procedure quality.[8] The system can also perform functions such as cutting, needle insertion, irrigation, and microsurgical cauterisation.

Safety issues in robot assisted surgery; focus on telesurgery

However, the safety of telesurgery is dependent on the experience of the surgeon and the performance capacity of the machine used. For instance, a study investigated the efficacy of the use of telesurgery in the removal of a phantom pituitary tumour in Nashville, by controlling a robot that was located about 800 kilometres away from the hospital. With a video latency of less than 100ms for the robot, all the surgeons involved in the operation gave it a perfect subjective safety score. However, they also noted that the operation used a dedicated network to ensure telecommunication is uninterrupted during the duration of the operation.[9] This is important, because intrinsic latency in telecommunication network determines the potential for risks, slips in operation, and other safety issues, even with expert surgeons, as a delay in relaying real-time video data could result in an incision made earlier or later than expected.[10] Whilst researchers note that expert surgeons could adapt to the delays, the safety of telesurgery deteriorates mildly at latencies of up to 200ms and increases exponentially to become fatally unsafe at above 1000ms.[11,12] Thus, prevention of damage to the nervous system during telesurgery require a dedicated high capacity network to ensure videos are displayed within the latency of 0-100ms and the surgeon is skilled in the procedure.

Safety mechanisms through machine learning: perception, haptic feedback, collision detection

The surgeon's perception is a major challenge to surgical safety. Typically, most experienced surgeons use the tactical sense between their instruments and the bones or tissue to guide them in neurosurgery. Yet the use of the sense of touch is eliminated with telesurgery and requires the surgical procedure to be steered purely with vision. Especially for the beginner, but also during complex procedures, this is an aspect that could increase the risk of slips or misdirection of the robot. How then, can this setback be overcome?

Although presently the technology is in the testing and experimentation state, haptic feedback should be integrated into telesurgery to address the issue of substituted contact for pure vision.[6] In practice, the haptic feedback is achievable through a combination of collision detection algorithms for the calculation of depth penetration, and through coordinate transformation between the various systems in the machine that is translated into a virtual wall which the surgeon can visualise on a monitor. Presently, the technology allows robots to have an 'intrinsic' force or deflection-based sensing mechanism that mimics haptic feedback, with the development of robots such as SIROMAN system. This uses haptic guided telesurgery for tumour removal. The robot was developed to allow surgeons to access tumour tissue located deep in the brain and remove it with minimal damage by the creation of a virtual wall-based haptic guidance. Haptic mechanisms restrict the autonomy of surgeons by solely allowing machine movement within the virtual walls. In other words, machine learning has made it potentially possible for modern robots to perform surgeries with the same accuracy as human beings. Thus, in the next two decades, higher safety standards could be guaranteed in telesurgery.

Robots in neurosurgery in the near future

The role and function of robots in neurosurgery in the future is dependent on the advancements of main stakeholders such as engineers, healthcare administrators, surgeons, entrepreneurs, and the public. Although the pace of technological development could theoretically cause the ultimate replacement of surgeons, it is unlikely to happen soon.[13]

The fact that the potential interaction between the computer, the patient, and surgeon has not been exploited, is mainly due to ethical and safety issues, which will also delay the replacement of the human factor in operations in the near future.[14] Even if biomedical engineers develop fully automated robots that can replace surgeons, the failure to change the public perception about the safety issues associated with machines compared to the decision-making processes of surgeons as human beings, could obstruct their adoption in hospitals;[15] furthermore, with the development of fully autonomous systems, fewer prac-

ticing surgeons have updated their practice and knowledge to be able to operate the machines currently, a trend that could hinder complete automation in the future.[16] Moreover, existing regulatory bodies in neurosurgery focus on the human behaviour rather than the success rate of robots, chiefly due to the difficulty involved in defining and classifying robotics. This signifies that surgeons will remain relevant in operations for the foreseeable future, with the next two decades witnessing a change in neurosurgery founded on the surgeon-robot-patient axis, with each stakeholder assuming joint custodianship of surgical operations.

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Brainstorm – Detective Stories from the World of Neurology

Author: Suzanne O'Sullivan
Published by: Penguin 2018
Price: £9.99
Pages: 352
ISBN: 9781784741310
Reviewed by: Mariam Shahid and Athea Ashley, Medical Students, University of Liverpool.

As medical students, the two of us are in a state of transition. We are on the way to identifying ourselves as doctors, but not quite there yet. Many things medical have been de-mystified for us, but others remain mysterious. And in her book, Suzanne O'Sullivan offers diverse and detailed insights into one such mystery, that well-known but often misunderstood condition – epilepsy. Acknowledging the many unknowns, she describes how clinical neurologists, even with all the modern advances in technology, continue to rely on traditional principles of medical practice to discern the diagnosis from complicated stories that patients may offer.

Her book is a collection of rare cases, where epilepsy manifests in its most elaborate and unusual forms. Yet with her methodical explanations of the patients' stories, the reader is able to follow each case through and understand the sequence of events. The descriptive illustrations of brain anatomy form a valuable visual aid, helping readers to contextualise structure in its clinical relevance. Every story unfolds clearly and chronologically, before readers' eyes, allowing them to perceive the patient's journey and its challenges, as well as challenges facing the medical professionals. Throughout the book, Dr O'Sullivan successfully de-mystifies and humanises 'the doctor', openly discussing the limits of her own knowledge and the limitations of Medicine in general – the Science yet to be discovered, the Technology yet to be invented. In her own words, "I was clutching at straws and we both knew it", when talking about one of her consultations.

Although only twelve cases are described, each one offers such a distinctive presentation that the book provides a comprehensive and aesthetically-satisfying picture of epilepsy. That the effects of epilepsy are not limited to convulsive seizures is highlighted. Symptoms other than witnessed convulsions are included, but also described are the more personal effects that epilepsy may have on patients and those closest to them. The depth with which their lives are portrayed, from actions that could cause embarrassment to those that might cause danger, affords patients the same humanity and sincerity as Dr O'Sullivan gives to the medical position.

The author's care for her patients shows in the portrayal of their cares and emotions: she makes the reader care too and care to know what she has to say as an author. But her passion and love of the scholarship of her subject is also evident; as she describes the brain in detail, she continues to draw the reader in – 'the nervous system is beautiful. It is intricate.'

Something which the book does not tackle is the most common expressions of epilepsy, and to a reader with little previous understanding of this condition, simply focusing on the rarer cases could leave them with a skewed perception: this book does not tick the box for epilepsy in the medical school curriculum, but was never intended to.

By contrast, Dr O'Sullivan explains each case with the assumption that her reader has no previous medical knowledge – good both for medical students and for non-medical students! Each time medical jargon is used, it is clarified, thereby expanding the readership able to engage in her work. In addition, analogies are used deftly to improve the book's comprehensibility, such as, '...staring at an MRI scan tells you no more about how the brain works than staring at a computer's circuitry tells you about how a computer processes information'. They also improve the book's readability.

This book may be a collection of individual histories, but it reads as a story of the brain, and an introduction to the most daunting of organs. It is engaging and thoughtful. It humanises epilepsy, a condition that has been associated with demonic possession, attacks from God, and many other myths and prejudices. Supernatural misconceptions are mercifully rare in Western society today, but other misconceptions and prejudices persist. Dr O'Sullivan's humane treatment of Epilepsy as a subject and of those affected by it or involved with it, isn't exactly 'brainstorming', but was genuinely mind-broadening for us.

As her book will have a popular readership, it definitely represents good value for money but was also time well-spent, at least at our level of Medicine.

Georges Gilles de la Tourette. Beyond the eponym

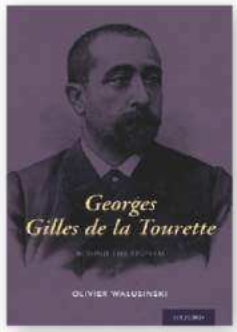
Perhaps because of its euphony, the name of Georges Gilles de la Tourette often becomes embedded in the neurological consciousness at an early stage of clinical training, the more so from the association of his syndrome of motor and phonic tics with coprolalia, scatology being particularly memorable for some reason. But who knows anything about the man, other than perhaps his association with Charcot and the Salpêtrière school?

Olivier Walusinski has a long established interest in this history of neurology in 19th century France (as well as of Yawning), manifest in many journal publications. In this volume he shares his research into the life of GGdelaT, and it is a fascinating story: for example, how many neurologists can claim to have survived attempted assassination (in 1893)? For those with an interest in etymology, there is a helpful explanation of why the amputation to "Tourette" syndrome is incorrect, since based on a toponymic; if abbreviation is required, "Gilles" syndrome would be more appropriate.

By far the longest chapter in the book is, appropriately, devoted to the eponymous syndrome. I was always perplexed that the original report of 1884 (previously translated by Lajonchere et al, Arch Neurol 1996;53:567-74) was ostensibly devoted to startle syndromes ("jumping" of Maine, latah of Malaysia, and myriachit of Siberia) but it transpires that the tic disorder was then conceived to be related to these other disorders of excessive movement.

In addition, Walusinski gives a contextualised analysis of many of the other major publications, including a treatise on hysteria. Clearly Gilles de la Tourette was an indefatigable writer, also interested in biography (he wrote a work on the pioneer French journalist Renaudot). He himself had extensive interactions with journalists (not least to promote his own career) and wrote occasionally for the lay press under the nom de plume of Paracelsus. To what extent developing neurosyphilis may have contributed to some of his self-promoting actions ("megalomania") remains speculative.

Anyone interested in the origins of clinical neurology in late 19th century France will want to read this scholarly volume, which is well presented with many illustrations from the author's personal collection. There are a few niggly errors (e.g. Helmotz, p.186, is presumably Helmholtz, they share the same dates; Lucerne, p.112, should perhaps be Lausanne; figure numbers inconsistent with text in Chapter 8).



Author: Olivier Walusinski
Published by: Oxford University Press, 2019.
Price: £29.99
Pages: 490
ISBN: 9780190636036
Reviewed by: AJ Larner, Cognitive Function Clinic, WCNN, Liverpool.

To list your event in this diary email Rachael@acnr.co.uk by 31st Aug 2019

2019

JUNE

Training in Behavioural Treatment for Tics (CBIT)
27-28th June, 2019; London, UK
E. Seonaid@tourettes-action.org.uk
www.tourettes-action.org.uk

The 5th EAN: Neuroinflammation – Science. Synergies. Solutions.
29 June-2 July, 2019
www.ean.org/Oslo2019

JULY

Endoscopic Anterior Skull Base Surgery: Hands-On Cadaveric Course
Monday 1st & Tuesday 2nd July 2019; Leeds, UK
www.aesculap-academia.co.uk
E. kimberley.cowley@aesculap-academy.com

British Neuro-Oncology Society Annual Meeting
3-5 July, 2019; London, UK
www.bnos.org.uk

The Co-Morbidities of Epilepsy
5 July, 2019; St George's, London, UK
http://ow.ly/b1pU30oj6Hp

MS Service Provision in the UK 2019: Raising the Bar
8 & 9 July, 2019; Birmingham, UK
multiplesclerosisacademy.org

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Neurotoxicity, Late effects, Rehabilitation & Ethics
11 July, 2019; NHNN, London
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/neurooncology

SEPTEMBER

Building the future of childhood brain injury: where do we go from here?
Friday 6 September, 2019; London, UK
www.thechildrenstrust.org.uk/conference

David Marr 50 Years On – Satellite meeting to 7th Cambridge Neuroscience Symposium
11 September, 2019; Cambridge, UK
www.neuroscience.cam.ac.uk/events/ABC2019/

7th Cambridge Neuroscience Symposium 2019
12-13 September, 2019; Cambridge, UK
www.neuroscience.cam.ac.uk/events/ABC2019/

British Neurotoxin Network (BNN) Annual Meeting 2019
12th-13 September, 2019; Lady Margaret Hall, Oxford, UK
www.neurotoxinnetwork.org
E. info@neurotoxinnetwork.org

Tourettes Action Research Network (TARN) meeting 2019
Friday 13 September, 2019; 9.30-4.30, London, UK
www.tickettailor.com/events/tourettes-action/222723

ILAE British Branch 17th Specialist Registrar Epilepsy Teaching Weekend
14th-15th September 2019
Oxford Mathematical Institute, Oxford
www.epilepsyteachingweekend.com

Frontiers in Traumatic Brain Injury 2019
16th September, 2019; London, UK
www.frontiersintbi.com

Parkinson's Academy: Parkinson's Foundation Masterclass
19 & 20 September 2019; Halifax Hall, Sheffield, UK
https://parkinsonsacademy.co/events/parkinsons-foundation-masterclass-37f

Royal College of Psychiatrists Faculty of Neuropsychiatry annual Conference
Thursday 19 and Friday 20 September 2019, London, UK
www.rcpsych.ac.uk

British Peripheral Nerve Society Autumn Meeting
Friday, 27 September, 2019; 10.00 - 17:00, London, UK
E. BPNS Administrator (Alexandra McWilliam) – secretariat@bpns.org.uk

OCTOBER

Joint meeting of the Society for Research in Rehabilitation and the British Society of Rehabilitation Medicine
14-15 Oct 2019, 2019; University of Warwick, UK
www.srr.org.uk

ILAE British Branch Annual Scientific Meeting
2nd-4th October 2019; Birmingham Conference and Event Centre, Birmingham
www.ilaebritishconference.org.uk

NOVEMBER

MSologists MasterClass
Module 1: 6-8 November 2019
Module 2: 21 & 22 May 2020; Sheffield, UK
multiplesclerosisacademy.org

The British Neurosurgical Research Group Meeting
Thursday 7 & Friday 8 November 2019; Edinburgh, UK
www.aesculap-academia.co.uk
E. kimberley.cowley@aesculap-academy.com

Bi-annual ESNA Non-Medical Prescribing Day
15 November, 2019; Liverpool, UK
Book via E. carrie.a.burke@wwl.nhs.uk.

Expert to Expert: Epilepsy For paediatric neurologists and other seeing children with epilepsy at tertiary level
28-29 November, 2019; Manchester, UK
https://courses.bpna.org.uk/ecomm_product_view.php?courseid=393

Dementia MasterClass
28-29 November, 2019; Halifax Hall, Sheffield University Campus, UK
https://dementiaacademy.co/events/dementia-masterclass-6/
T. 0114 327 0230

DECEMBER

Encephalitis Conference 2019
2 December, 2019; Royal College of Physicians, London, UK
www.encephalitis.info/conference2019

Liverpool Paediatric Neurosurgery Masterclass
Thursday 5th - Friday 6th December 2019; Liverpool, UK
www.aesculap-academia.co.uk
E. samantha.womack@aesculap-academy.com

17th Annual King's College Neuromuscular Disease Symposium

Conference details: 25th January 2019, London, UK. ***Report by:*** Dr Kiran Samra, Neurology Registrar, Guy's and St Thomas' Hospital. ***Conflict of interest statement:*** None declared.

Whether you're a Consultant Neurologist hoping for an update, a trainee eager to bypass laborious peripheral nerve and muscle chapters, or a physiotherapist keen to better understand patients, this conference has something for everyone. Although in previous years the symposium provided niche talks aimed at neuromuscular specialists, in recent years it has provided a more practical approach targeting a wider audience.

Not only is it my most affordable study leave request (to the relief of my line manager), but every year I leave with useful nuggets of information for my next clinical encounter with a nerve or muscle patient. I also leave thinking "I really should know this, thank goodness I came". This is my third year in a row attending the King's College Neuromuscular Disease Symposium, and I will continue to do so until HEE remove it from the 'mandated/optional course' list.

Established in 2001, this conference is held annually in the stylish Fetal Medicine Research Institute, a stone's throw from the station. Seats are comfy with plenty of leg room, and there's fresh fruit, croissants and a nice tea selection to see you through the day (and coffee of course).

Dr Rob Hadden, Consultant Neurologist, Vice President of the British Peripheral Nerve Society and Lead for the Regional Peripheral Nerve Service at King's, kick-started the day with a talk on vasculitic neuropathy. My first nugget of information appeared in the first slide – we are taught endlessly about CIDP but vasculitic neuropathies are actually commoner than CIDP, and nerve biopsy is the gold standard for diagnosis.

Then, as if you needed reminding that you probably shouldn't have had that extra pain au chocolat, Dr Abd Tahrani, NIHR Clinical Scientist and Honorary Consultant Endocrinologist in Birmingham, reminded us that diabetes is the leading cause of neuropathy globally and that almost 30% of those with prediabetes have a painful neuropathy. Interestingly (my second nugget), obstructive sleep apnoea, which we know is associated with obesity, is more likely in those with insulin resistance, and can itself cause peripheral neuropathy. It appears that obesity and insulin resistance, as well as hyperglycaemia can cause nerve damage.

As more cancer drugs are fast-tracked through the NHS, more horrific side effects seem to be emerging. Dr Sarah Flatters, Senior Lecturer at KCL, gave a much-needed talk on chemotherapy-induced peripheral neuropathy. As well as an overview of the clinical presentation, prevalence and treatments, Dr Flatters stunned the audience with her research outlining causal mechanisms and a possible biomarker to identify susceptible patients. My third nugget was learning duloxetine is the only agent associated with a positive outcome in these patients, and that cold allodynia is a key chemotherapy-related neuropathy symptom.

Complex regional pain syndrome (CRPS) and fibromyalgia were boldly tackled by Dr David Andersson, Clinical Scientist at KCL. This compelling talk proved a useful introduction and my fourth nugget – we can treat CRPS with plasmapheresis. This has been shown to improve CRPS symptoms, which coincides with the emerging concept that CRPS involves sensitisation of nociceptors by autoantibodies, as shown in mouse models. Although there is no effective treatment, fibromyalgia appears to involve similar mechanisms.

If neurophysiology is your thing, the vibrant talk on antibody-mediated nodo-paranodopathies in GBS and CIDP variants by Professor Antonino Uncini from D'Annunzio University of Chieti-Pescara, Italy, captured the audience. His explanation of mechanisms of nerve injury, electrophysiological and pathological findings, and how to avoid misdiagnosis, were particularly interesting.

As mentioned, this conference is cost effective, however, we were spared the budget sandwiches filled with questionable contents and given a variety of fresh food options. In fact, I went back for more, not because it was free (although this certainly helps), but because it was genuinely tasty.

http://www.spiraliseurope.com/projects/fetal-medicine-research-institute/

After lunch, Mr Henry Willmott, Consultant Orthopaedic Surgeon at Conquest Hospital in Hastings, gave a spirited and surprisingly entertaining talk on musculoskeletal foot and ankle pain. Neurology referrals for foot pain are common, and Mr Willmott gave us a clear, pragmatic approach we can apply to practice. Cavovarus foot deformity that causes pain, can occur secondary to balance and proprioception issues, and spasticity and weakness, all commonplace in a neurology setting. I have a better grasp of when I should refer to orthopaedics, and plan to practice the foot exercises he demonstrated to avoid a foot deformity of my own!

Let's not forget those 'case presentation' learners out there. Dr Charlotte Dougan, Consultant Neurologist at the Walton Centre in Liverpool, presented a case on riboflavin-responsive neuromyopathy due to multiple acyl-CoA dehydrogenase deficiency. Jo Reffin, physiotherapist at King's, presented an interesting case of the services involved in facilitating a successful pregnancy in FSHD. Dr Mohamed Mahdi-Rogers, Consultant Neurologist at King's, presented a patient with refractory painful neuropathy who, after skin biopsy and microneurography, was found to have CASPR2 antibody-mediated disorder.

Dr Michael Rose, Consultant Neurologist at King's, provided valuable insight into successful assessment and management of referrals to the muscle clinic with fatigue. Naturally, the nemesis chronic fatigue syndrome (CFS) was mentioned (for the first time Lyme was not brought up, thankfully) and, I learnt that cognitive behavioural therapy is worth considering for negative thoughts about fatigue in all cases, and not just CFS.

The day ended with a captivating talk by Dr Stefan Brady, Neuromuscular Consultant at Southmead Hospital in Bristol, on recent developments in muscle disease. This is an exciting area of neurogenetics and gene therapy gives hope to those with hitherto untreatable conditions.

Key points

1. Nerve biopsy is the gold standard for diagnosis of vasculitic neuropathy.
2. Obstructive sleep apnoea may cause peripheral neuropathy – sleep pattern should form part of history-taking.
3. Duloxetine is worth a try in chemotherapy-induced neuropathy patients.
4. Plasmapheresis may help complex regional pain syndrome symptoms.
5. A conference doesn't need to be expensive to provide a decent lunch.

Lewy Body UK Meeting 2019

Conference details: 7th June, 2019, Newcastle, UK. ***Report by:*** Angeliki Zarkali, Alzheimer's Research UK Clinical Fellow, Dementia Research Centre, UCL and ABN Trainee Committee Secretary. ***Conflict of interest statement:*** None declared.

The inaugural Lewy Body UK meeting brought together clinicians and researchers in the field of Lewy Body Disease across the UK. The inaugural meeting was appropriately held in Newcastle, whose university has a long and prolific history in Lewy Body research and brings together substantial clinical and research expertise. Although chilly, there was sunshine, interesting talks and plenty of time to exchange ideas over coffee; well worth the train ride north!

The meeting itself covered aspects of Lewy Body Disease from bench to bedside, from national and international experts. After a welcome by Dr John-Paul Taylor from Newcastle University, which set the scene to the day, followed a session on *Discovery and bioscience*, chaired by Dr Rimona Weil, University College London. Dr Daniel Erskine, Newcastle University gave a comprehensive overview of the pathology of Lewy Body Disease, focusing on the role of different alpha synuclein strains in the pathogenesis of the disease. Dr Allison Yarnall, Newcastle University, followed with a talk on autonomic symptoms in Lewy Body Disease; she walked us through the mechanisms and most importantly the investigations and clinical management of these challenging and often unappreciated symptoms.

Next there was a session on *Visual hallucinations*, chaired by Dr Claire O'Callaghan, University of Cambridge. Dr Dominic Ffytche, Kings College London, covered the recent models of hallucinations and highlighted the importance of detailed phenomenology of hallucinations in research studies. He then reported results from the SHAPED study showing differences in the prevalence of misperceptions and illusions compared to that of complex visual hallucinations across different dementias and eye disorders. Next, Dr James Shine, University of Sydney, gave a riveting talk on the neuroimaging of visual hallucinations. He discussed how attention governs cognition and evidence from recent research that disruption of attentional networks occurs in patients with Lewy Body Disease who experience visual hallucinations. Finally, Dr Daniel Collerton, Newcastle University, walked us through a predictive coding model of visual perception and discussed different theoretical models of visual hallucinations.

After exciting discussion with colleagues across the UK during lunch, we returned for the last session of the day on *Diagnosis and Treatment*, chaired by Professor Ian McKeith, Newcastle University. Professor Alan Thomas, Newcastle University gave us a valuable update on the diagnostic criteria for the disease and the DIAMOND assessment toolkits; these will soon become publicly available and will be undoubtably a most useful clinical resource in assessing and managing patients with Lewy Body Disease. Next, Riona McArdle, Newcastle University, presented the results of her research into gait changes in early Lewy Body Disease and how wearable technology and gait assessment could aid earlier diagnosis of these patients. In the last talk of the day, Professor John O'Brien, University of Cambridge, gave an overview of the regional variation in identification and management of patients with Lewy Body Disease presented the results of the recent Diamond-Lewy study, soon to be published.

Overall, Lewy Body UK 2019 was an amazing meeting with a wealth of scientific and clinical presentations covering the whole breadth of Lewy Body Disease as well as ample networking opportunities. A great first meeting that definitely has set the bar high for future events. The next Lewy Body UK meeting will be held in University College London, 12th June 2020; I am definitely looking forward to it!

Dementias 2019

Conference details: 14th and 15th of February 2019, Cavendish Conference Centre, London, UK. ***Report by:*** James Cranston, Freelance Medical Writer.
Conflict of interest statement: None declared.

Dementias 2019, the 21st National Dementias conference hosted by MA Healthcare Conferences was successfully held on the 14th and 15th February at Cavendish Conference Centre in London.

More than 150 participants across the country attended the conference, including 21 speakers and a new addition of poster presenters who shared their research, initiatives and experiences in the fields of psychiatry, geriatrics and neurology.

Professor Alistair Burns, National Clinical Director for Dementia and for Mental Health in Older People at NHS England together with Professor John O'Brien, Professor of Old Age Psychiatry at the University of Cambridge opened the conference by highlighting its focus. This was to 'improve dementia diagnosis and research quality' and to 'improve awareness and management of lesser known dementias'. Professor O'Brien noted that 'to provide an ideal dementia service, we need to include the expertise from geriatricians, neurologists and psychiatrists and indeed non-medical people involved in the care of those with dementia.'

We kicked off the first day with a keynote address on 'The UK Dementia Research Institute', delivered by its Associate Director Professor Giovanna Mallucci. This initiative aims at accelerating the discovery of new treatments and better care for people with dementia by focusing research on how dementias develop and progress. Professor John Schott, Professor of Neurology at the Dementia Research Centre at UCL followed by sharing his research on CSF biomarkers. Professor Schott gave insights into the clinical interpretation of CSF biomarkers, how CSF analysis is being implemented into the NHS and emphasised the potential for analysing future biomarkers.

The next talk covered the 2018 NICE dementia guidelines on diagnostic imaging and was held by Professor John O'Brien, a member of the advisory committee to NICE. Later in the morning, Dr Matthew Jones was joined by Dr Jennifer Thompson to deliver an interactive case presentation, inviting the audience to share their thoughts and processes on dementia diagnosis.

The afternoon session began with Dr Greta Rait considering the current state of dementia assessment, recognition and prevention in primary care. This was followed by Alex Ruck-Keene sharing his thoughts on the Deprivation of Liberty Safeguards and the upcoming Mental Capacity Amendment Bill. The next speaker, Professor Dag Aarsland, Chair of Old Age Psychiatry at King's College in London shared exciting evidence focusing on the treatment of behavioural symptoms in dementia. After, Professor Roy Jones gave a compelling overview of the history of NICE. He explained the challenges of measuring clinical and cost effectiveness for dementia treatments and how NICE is incorporating more clinical experience as well as hard evidence. The day concluded with a lively discussion about where dementia care and treatment might shift in the next 5 years and the importance of a combined approach amongst specialists in dementia diagnosis.

The second day of Dementias 2019 opened with a keynote address titled 'What can epidemiology can tell us about dementia?'. Professor Carol Brayne, Professor of Immunology at the University of Cambridge presented compelling evidence that our dementia service needs to be tailored to consider the whole life of the patient, including cognitive lifestyle and multi-morbidities. The following session was delivered by Professor Julian Hughes, who balanced the ethical issues of surrogate decision making, sex and euthanasia with his research and rights of people with disabilities. Dr Iracema Leroi then shed light on the importance of recognising and managing hearing loss and visual loss as co-morbidities of dementia. Later in the morning Dr Emma Vardy, Clinical Dementia and Delirium Lead at Salford Royal NHS Foundation Trust gave a fascinating talk on diagnosing and managing delirium. She emphasised that delirium needs a combined approach to treat appropriately and equipped specialists with some tools to implement delirium assessment in their areas.

Dr Liz Simpson launched the afternoon session with a presentation on the importance of palliative care in dementia. She shared research on the of benefits of specialist assessment at memory clinics and called for more end of life support from geriatricians, psychiatrists and neurologists. Professor Linda Clare then delivered a speech titled 'Psychosocial interventions in dementia'. The next speaker was Professor Louise Robinson who lectured on the role of the GP in post diagnostic care of dementia. Professor Gill Livingston closed the conference with an inspirational presentation from The Lancet Commission. Meta-analyses of global dementia prevalence and lifestyle risk factors were used to remind us of the enormous effect modifying these risks could have on the global burden of dementia.

'Dementias 2020' will be held at the Cavendish Conference Centre in London on the 13th and 14th February 2020.

European Academy of Neurology Autumn School 2018

Conference details: 8th to 11th November 2018, Loutraki, Greece. ***Report by:*** Dr Duncan Street, Neurology ST4, West Midlands.
Conflict of interest statement: None declared.

Between the 8th-11th November 2018, I was fortunate enough to escape the dull, dark and dreary depths of the UK winter to join 59 other colleagues in training from across Europe and beyond to participate in the inaugural European Academy of Neurology (EAN) Autumn School in Loutraki, Greece hosted by the Hellenic Neurological Society. This meeting, following in the established footsteps of the EAN Spring School, aimed to deliver a practical course incorporating didactic, lecture-based morning sessions with interactive, case-based afternoon sessions using suitable patients identified by the local clinician leads for the course. Each of the three full days were given a different theme – Episodic loss of consciousness, Gait dysfunction and Tremors respectively – and were provided by multiple consultant experts in each of these fields. Even more luckily for me given my limited foreign language skills, the whole course including the exit exam was to be delivered in English!

Although torrential rain greeted my arrival at Athens airport, the heavens were to clear for the rest of the course with mild late autumn sunshine and some fantastic sunsets framing the low-season Greek holiday resort of Loutraki. After a warm greeting on the opening night by Professor Hannah Cock (St George's University, London) then head of the EAN Education Committee and representatives from the Hellenic Neurological Society and the EAN Education team, the lectures started bright and early the following morning. Professor Cock, Dr Anastasios Bonakis (University of Athens) and Dr Tim von Oertzen (Linz, Austria) provided a whistle-stop but comprehensive review to the vast topic of episodic loss of consciousness, covering the approach to differential diagnosis and utility of investigations and other psychiatric and psychological assessments. The practical sessions in the afternoon allowed clarification of points introduced earlier in the day by a broad collection of patient-videos and concurrent EEG recordings, each of the three following a one-hour round-robin format with short coffee breaks in-between to retain alertness. Particular focus was placed on narcolepsy, cataplexy, parasomnias and unusual seizure syndromes of the frontal and temporal lobes – areas I had previously had little exposure to during my fledgling clinical career. This was followed in the evening by entertainment in the form of a moonlit boat trip along the historic Corinth Canal and a traditional Greek dancing display and dinner at a local hotel restaurant. Despite protestations from those around me I refrained from exposing my new colleagues to my terrible dancing once the opportunity arose to 'join in' later in the evening!

The next day moved onto the topic of 'Gait dysfunction' and was provided by Professor Espen Dietrichs (University of Oslo), Professor Leonidas Stefanis (University of Athens) and Dr George Koutsis (University of Athens). These sessions again provided a broad overview to include approach to history and examination, investigation of gait apraxias and classification and investigation of cerebellar ataxias with Professor Dietrichs' common gait disorder imitations and references to John Cleese particularly memorable. This was followed in the afternoon by further excellent video cases on normal pressure hydrocephalus and a local patient diagnosed with Freidreich's ataxia who kindly tolerated numerous examinations over the course of the session with good grace. Evening entertainment took the form of a friendly and inclusive scientific dinner with highlights including additional fascinating case presentations from the faculty and an interesting interactive quiz by Professor Dietrich.

The final day was dedicated to 'Tremors' with Professor Carlo Colosimo (Terni, Italy), Professor Maria Stamelou (University of Athens) and Professor Joaquim Ferreira (University of Lisbon, Portugal) the illustrious faculty covering the topics of classification, investigation and treatment. Video sessions and another kind patient with Parkinson's disease giving up her Sunday allowed the pertinent defining points raised in the morning to be immediately reinforced by clinical application with Professor Stamelou's enthusiasm for her subject proving particularly infectious. The exit exam swiftly followed including a number of questions directly derived from lectures earlier in the course with the final evening farewell party lasting into the early hours of the morning.

It was with some sadness that I bade farewell to my European colleagues the next day – I have made a number of friends and look forward to catching up with them at future events. In a time of increasing uncertainty regarding the position of the UK within Europe I was delighted to be able to attend this excellent course with the costs for accommodation, board and materials covered via the EAN with delegates only funding the cost of travel to Athens. We discussed similar clinical challenges facing us despite many miles and technological degrees of separation between us. In the ancient land of myths and legends I hope it is not too fanciful to think that even if Brexit does succeed in driving a political wedge between us and our continental partners, such a well-run and valuable course will be available to attend for future interested UK trainees. Following its success, it has recently been announced that there will be at least another year commissioned for November 2019 again in Athens – it would appear that the birthplace of civilisation has more to offer intrepid minds willing to take up the challenge!

Young Epilepsy launches urgently needed, 'Online Guide for Schools' for education professionals

The charity, Young Epilepsy, has launched a new online resource for education professionals, which provides access to information and practical tools enabling them to better support the children with epilepsy who are under their care. The resource was funded by an educational grant by Veriton Pharma.

A survey of 600 adults working in the education sector was commissioned by the charity, and found that four in 10 education professionals would not be able to help a student having an epileptic seizure.

Two-thirds of those polled have had no training about how to support the children with epilepsy in their care, including what to do in the event of a seizure.

Other results confirmed that only 29% knew that they should time the length of seizure and a third confirmed they wouldn't know when to call for an ambulance in the event of a seizure. Experts recommend you ring 999 if you know it's their first seizure or if the seizure lasts for more than five minutes as prolonged seizures can result in status epilepticus, a potentially fatal condition.

Mark Devlin, Chief Executive of Young Epilepsy said: "We know that our colleagues

working in any education setting are facing many challenges every day, and most are doing a fantastic job in ensuring that every child in their care is being fully supported. But these latest figures show that children with epilepsy are struggling to have their conditions fully understood by the people who are playing an essential role in their educational and emotional development."

The Online Guide for Schools contains essential information for anyone working with young people who have epilepsy and is available to access completely free of charge at www.youngepilepsy.org.uk/guideforschools.

Encephalitis Conference 2019

2nd December, Royal College of Physicians, London

CALL FOR ABSTRACTS OPEN

There will be prizes and certificates awarded on the day. Deadline: 31st July 2019

Abstracts should be related to encephalitis and will be considered in any field or subject area.

The Encephalitis Conference is the only event in the world dedicated exclusively to encephalitis. It brings together professionals with various expertise and knowledge, ranging from aetiology, pathogenesis, and diagnosis, to treatment, recovery and rehabilitation of people affected by encephalitis.

www.encephalitis.info/conference

Neurological Alliance Report shows increasing number of neurological cases

The Neurological Alliance has recently published a new report, Neuro Numbers which shows that the number of neurological cases has now reached at least 14.7 million in England. This equates to more than one in six people living with one or more neurological conditions. The report also highlights that the prevalence of neurological conditions will continue to increase due to an ageing population, improvements in diagnosis and advances in neo-natal care.

In response to this new data, The Neurological Alliance is calling for neurology to be prioritised by the health and care system to ensure the needs of this growing patient group are met.

75,000 neurological cases per Clinical Commissioning Group (CCG)

Analysis of the new data reveals that there are over 75,000 neurological cases per Clinical Commissioning Group (CCG). Data produced by NHS RightCare for local and regional commissioning areas demonstrate there is a substantial financial savings opportunity in relation to reducing emergency admissions and bed days with a mention of a neurological condition. Yet a recent audit of CCGs, undertaken by The Neurological Alliance has demonstrated that only 35 out of 195 CCGs have delivery plans that include neurological conditions.

Sarah Vibert, Chief Executive of The Neurological Alliance said: "Our latest Neuro Numbers report shows that the number of people living with neurological conditions has grown over the last five years and will continue to increase. We were dismayed to find that the NHS Long Term Plan did not mention the word 'neurology'. What is needed is increased awareness of neurological conditions among those responsible for planning services. But without any national neurological priority, many of the measures set out in the NHS Plan that have the potential to ensure people with neurological conditions are better supported may not bring about the changes needed."

National incentives for local decision makers

We are calling for the different parts of the health system to work together to address the issues being highlighted by the data. The report highlights that 2019 is set to be a landmark year for our understanding of neurological services, with Getting it Right First Time due to report on neurology in the summer. We would like to see the introduction of national incentives for local and regional decision makers to tackle unwarranted variation in neurological care, based on the opportunities for improvement demonstrated by local-level data.

Katharine McIntosh, Senior Policy Advisor from The Neurological Alliance said: "The system needs to act now to address the issues the data is flagging. A year ago, it was shown that deaths from neurological conditions are 35% more likely to be premature. We know that many of these deaths are potentially avoidable with better care. Mortality data also highlights that neurology is particularly adversely affected by health inequalities – for example mortality related to epilepsy in the most deprived areas was three times higher than in the least deprived areas. We are yet to see concerted action to tackle avoidable deaths related to neurological conditions."

Read the full report at https://www.neural.org.uk/resource_library/neuro-numbers-2019/

IQoro for stroke-related dysphagia

NICE has developed a Medtech Innovation Briefing (MIB) with advice to aid local decision making on the use of IQoro for stroke-related dysphagia. Concluding their in-depth study of the effectiveness of IQoro® in the treatment of the legacy of stroke, NICE judged it to be unique, innovative and that the intended place in therapy would be as well as standard speech and language therapy in people with stroke-related dysphagia.

In one of the scientific papers assessed and referenced by NICE in the bulletin, a group of patients with stroke that had suffered swallowing difficulties for up to ten years were treated with IQoro®. After 5 to 8 weeks' treatment, 97% had improved their swallow, and 63% regained a normal swallowing ability. This important news allows NHS staff to consider deploying IQoro® treatment in the post-acute, residential care, community care or domiciliary care phases as outlined by NICE in the MIB.

https://www.nice.org.uk/advice/mib175

Neurokinex funding facilitates bursaries to support children with paralysis

The Neurokinex Charitable Trust is now able to offer bursaries to children living with paralysis at its Neurokinex Kids centre in Gatwick thanks to receiving £20,000 in funding from The Peter Harrison Foundation Community Fund. The 'small grants fund' organisation supports local community and voluntary groups and this award is part of its 'Special Needs and Care for Children and Young People' programme.

The Neurokinex Kids Centre Sponsorship Fund will allow access to cutting-edge neurological rehabilitation for eligible children living with all forms of paralysis, including spinal cord injury, stroke, transverse myelitis and cerebral palsy.

Neurokinex is a leading, not-for-profit provider of activity-based rehabilitation. Established in 2013, it is the first and only International affiliate of the Christopher & Dana Reeve Foundation's NeuroRecovery Network®.

Please contact trustees@neurokinex.org for information on how to apply. www.neurokinex.org

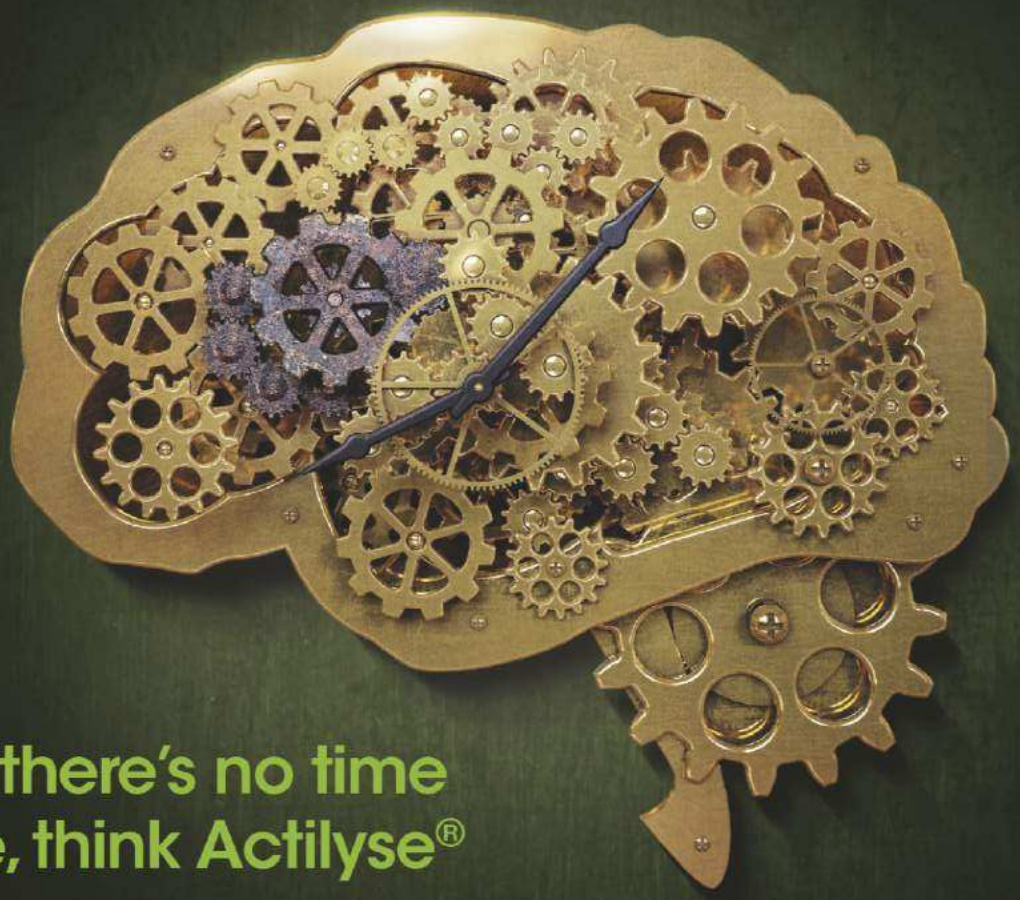
Improving management of headache, migraine and chronic pain

The Elective Care Transformation Programme's wave 5 100 Day Challenge ran from October 2018 to the end of January 2019, with neurology as one of the focus specialities. The programme used a structured innovation method that unlocks the knowledge and skills of frontline staff and service users to accelerate the pace of change across complex systems. Teams were challenged by their senior leaders to design and test interventions within 100 days to improve neurology services. Interventions were themed across the pathway to look at rethinking referrals, shared decision making and self-management support, and transforming outpatients.

Teams in North East Essex, Salford and South West Hampshire focused on improving the management of headaches and migraine. Improved referral pathways, provision of Advice and Guidance services for GPs and better access to community headache services contributed to reducing referrals to secondary care and waiting times for treatment. Liverpool chose to address chronic pain. The team trialled a community multidisciplinary team (MDT) and found the majority of referred patients could either be discharged to the GP with advice or were suitable for a community MDT appointment.

Learning from the neurology 100 Day Challenge has been collated in the neurology specialty handbook which covers an overview of tested interventions. The handbook, supporting webinars, case studies from pilot sites, further resources and useful information can all be found on the Elective Care Community of Practice online collaboration platform.

You can become a member of the Community of Practice by emailing: ECDC-manager@future.nhs.uk



When there's no time to lose, think Actilyse®

Make sure your eligible AIS patients don't miss out*[1]

Actilyse® significantly improves the odds of a good stroke outcome vs placebo or open control, regardless of age† or stroke severity‡, when delivered within 4.5 hours of symptom onset.[2]

Actilyse®: the gold standard of AIS therapy in the UK[3,4]

*Actilyse® is indicated for the fibrinolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.[1]
†When Actilyse® is considered for the treatment of acute ischaemic stroke in carefully selected adolescents ≥16 years of age, the benefit should be weighed carefully against the risks on an individual basis and discussed with the patient and parent/guardian as appropriate. Actilyse® can be used in patients >80 years on an individual benefit-risk basis. Patients of advanced age should be selected very carefully, taking into account both the general health and the neurological status.[1]
‡Actilyse® is contraindicated in patients with severe stroke as assessed clinically (e.g. NIHSS >25) and/or by appropriate imaging techniques.[1]

Prescribing Information (UK) – STROKE ONLY

ACTILYSE® (alteplase)

10mg, 20mg and 50mgx powder and solvent for solution for injection and infusion. Actilyse vials contain alteplase (recombinant human tissue-type plasminogen activator, t-PA) dry powder 10mg, 20mg and 50mg, supplied with water for injections. **Indication:** Fibrinolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible within 4.5 hours after onset of symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques. The treatment effect is time-dependent, therefore earlier treatment increases the probability of favourable outcome. **Dose and Administration:** Give as soon as possible within 4.5 hours of symptom onset. Beyond 4.5 hours there is a negative benefit risk ratio associated with Actilyse administration and it should not be administered. Total dose 0.9mg/kg (maximum 90 mg): 10% by iv bolus, remainder by iv infusion over 60 minutes. Avoid aspirin or iv heparin in the 24 hours after treatment with Actilyse. Paediatric population: There is limited experience with the use of Actilyse in children and adolescents. Actilyse is contraindicated for the treatment of acute ischaemic stroke in children and adolescents under 16 years of age. The dose for adolescents 16-17 years old is the same as for adults. **Contraindications:** Hypersensitivity to any constituent or gentamicin (a trace residue from the manufacturing process) and situations with a high risk of haemorrhage such as: significant bleeding disorder at present or within past 6 months, known haemorrhagic diathesis, effective oral anticoagulant treatment, manifest or recent severe or dangerous bleeding, known history of or suspected intracranial haemorrhage, suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm, history of CNS damage, within 10 days of traumatic arterial heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel, severe uncontrolled arterial hypertension, bacterial endocarditis, pericarditis, acute pancreatitis, documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, arterial/venous malformations, neoplasm with increased bleeding risk, severe liver disease, including hepatic failure, cirrhosis, portal hypertension and active hepatitis, major surgery or significant trauma in past 3 months, symptom onset more than 4.5 hours or symptom onset unknown and potentially more than 4.5 hours ago; minor neurological deficit or symptoms rapidly improving before infusion start; severe stroke; seizure at onset of stroke; evidence of ICH on CT-scan; symptoms of subarachnoid haemorrhage even if CT-scan normal; heparin within previous 48 hours and elevated thromboplastin time; history of stroke and concomitant diabetes; prior stroke within last 3 months; platelet count <100,000/mm³; systolic blood pressure >185 mm Hg or diastolic >110 mm Hg, or aggressive management necessary to reduce BP to these limits; blood glucose <50 mg/dl or >400 mg/dl (< 2.8mM or > 22.2mM); not indicated for patients under 16 years. **Warnings and precautions:** Situations where there is an increased risk of bleeding, including recent small traumas. The elderly are at increased risk of intracranial haemorrhage. Avoid rigid catheters. Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care and in the use of thrombolytic treatments, with the facilities to monitor. Risk of intracranial haemorrhage is increased in this indication, particularly in patients with: high risk of haemorrhage; small asymptomatic aneurysms of the cerebral vessels; pre-treatment with aspirin; treatment should not be delayed, can be used in patients over 80 years on an individual benefit-risk basis; carefully consider both the general health and the neurological status. Monitor BP, give iv antihypertensive treatment if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg. Immune-mediated hypersensitivity reactions associated with the administration of Actilyse can be caused by the active substance alteplase, gentamicin (a trace residue from the manufacturing process), any of the excipients, or the stopper of the glass vial with Actilyse powder contains natural rubber (a derivative of latex). There is also a risk of hypersensitivity reactions mediated through a non-immunological mechanism. Angio-oedema represents the most common hypersensitivity reaction reported with Actilyse. This risk may be enhanced in the indication acute ischaemic stroke and/or by concomitant treatment with ACE inhibitors. Patients treated should be monitored for angio-oedema during and for up to 24h after infusion. If a severe hypersensitivity reaction (e.g. angio-oedema) occurs, the infusion should be discontinued and appropriate treatment, which may include intubation, should be promptly initiated. The use of Actilyse may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely confirmed by appropriate test(s) of anticoagulant activity for the product(s) concerned showing no clinically relevant activity on the coagulation system (e.g. INR≤ 1.3 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal). Paediatric population: When Actilyse is considered for the treatment of acute ischaemic stroke in carefully selected adolescents ≥ 16 years of age the benefit should be weighed carefully against the risks on an individual basis and discussed with the patient and parent/guardian as appropriate. Adolescents ≥ 16 years of age should be treated according to the instruction in the label for the adult population after imaging by appropriate techniques to rule out stroke mimics and confirming arterial occlusion corresponding to the neurological deficit. **Interactions:** Coumarin derivatives, oral anticoagulants, platelet aggregation inhibitors, heparin, GPIIb/IIIa antagonists and other agents influencing coagulation increase haemorrhage risk. Concomitant treatment with ACE inhibitors may enhance the risk of a hypersensitivity reaction. **Fertility, pregnancy and lactation:** There is limited amount of data from the use of Actilyse in pregnant women. Nonclinical studies performed in doses higher than human doses exhibited foetal immaturity and/or embryotoxicity, secondary to the known pharmacological activity of the drug. Alteplase is not considered to be teratogenic. In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk. It is not known if alteplase is excreted into human milk. Clinical data on fertility are not available, nonclinical studies performed with alteplase showed no adverse effect on fertility. **Undesirable effects:** Very common (≥1/10): intracerebral haemorrhage represents the major adverse reaction in acute ischaemic stroke (up to 15% patients) – discontinue Actilyse if potentially dangerous haemorrhage occurs, bleeding from damaged blood vessels, recurrent ischaemia/angina pectoris, hypotension and heart failure/pulmonary oedema. Common (≥1/100 to <1/10): intracerebral haemorrhage (in the treatment of acute myocardial infarction and acute pulmonary embolism), pharyngeal haemorrhage, gastrointestinal haemorrhage, ecchymosis, urogenital haemorrhage, injection site haemorrhage, cardiogenic shock, cardiac arrest and reinfarction. Uncommon (≥1/1,000 to <1/100): pulmonary haemorrhage, epistaxis, ear haemorrhage, reperfusion arrhythmias, mitral regurgitation, pulmonary/other systemic/cerebral embolism, ventricular septal defect, blood pressure decreased. Rare (≥1/10,000 to <1/1,000): eye haemorrhage, pericardial haemorrhage, retroperitoneal bleeding, hypersensitivity reactions (e.g. rash, urticaria, bronchospasm, angio-oedema, hypotension, shock), embolism, nausea. Very rare (<1/10,000): Serious anaphylaxis, events related to the nervous system – often associated with ischaemic/haemorrhagic cerebrovascular events. Not known: Bleeding in parenchymatous organs, vomiting, body temperature increased, fat embolism, blood transfusions (necessary). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 1 x 50mg Actilyse plus transfer device £432.00; 1 x 20mg Actilyse plus transfer device £259.20; 1 x 10mg Actilyse £172.80. All packs also contain the appropriate quantity of water for injections. **Legal category:** POM. **MA number:** PL 00015/0120. **Marketing Authorisation Holder:** Boehringer Ingelheim Ltd, Ellesfield Avenue, Bracknell, RG12 8YS. Prescribers should consult the Summary of Product Characteristics for full prescribing information. See SPC for use in acute MI and acute PE. **Prepared in October 2018.**

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 Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

References: 1. Actilyse® Summary of Product Characteristics. Boehringer Ingelheim Ltd. Available at: http://www.medicines.org.uk/emc/medicine/308 (accessed April 2019). **2.** Emberson J *et al. Lancet* 2014;384:1929–1935. **3.** NICE Technology Appraisal 264. Alteplase for treating acute ischaemic stroke. October 2012. Available at: https://www.nice.org.uk/guidance/ta264/chapter/1-Guidance (accessed April 2019). **4.** RCP National Clinical Guideline for Stroke 2016. Available at: https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5i-(1).aspx (accessed April 2019).

AIS = acute ischaemic stroke; NIHSS = NIH Stroke Scale.

Boehringer Ingelheim

Actilyse® alteplase

Date of preparation: April 2019 PC-UK-100799