

# inspire

Autumn 2017

## Student Health Sciences Research Journal

### THIS ISSUE INCLUDES:

#### News & Features

Repetitive head  
injury in contact  
sports

Managing anxious  
patients in  
dentistry

#### Research & Reports

Faecal microbiota  
transplantation for  
C.difficile infection

Diagnosing and  
managing aortic  
dissection

*Plus more...*



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# The INSPIRE experience: a new student research journal, for students and by students

It is with great pleasure that we introduce you to Issue 2 of the INSPIRE Student Health Sciences Research Journal. We are delighted to share with you an outstanding collection of work by medical, veterinary and dentistry students from the universities of Cardiff, Plymouth, Exeter and Bristol.

The INSPIRE initiative provides medical school students with valuable research opportunities, including summer vacationship projects and taster days in a wide range of fields. Our journal aims to empower students in the discipline of research by providing a platform for students to advance their academic publication skills. This is especially important to ensure that the doctors, dentists and vets of tomorrow are adequately equipped with the skills that undertaking research can provide. Examples of such skills include critical appraisal, conducting audits, improving clinical practice and of course broadening their knowledge in their respective fields.

We have endeavoured to improve upon our previous Issue by publishing a range of pieces, from research on chronic traumatic encephalopathy to the welfare of orcas in captivity. With this variety of articles and topics, ranging from literature reviews to interviews, we hope to provide a colourful, interesting and relevant picture of current healthcare issues. We also aim to encourage our readers to have a wider appreciation for the many subfields of medicine, dentistry and veterinary science.

We are very grateful to the student authors, peer reviewers and senior editorial team who have worked diligently in creating this Issue, and wish to thank the INSPIRE Leads and all others involved who have helped make this Issue possible.

We hope you enjoy reading the journal as much as we have enjoyed creating it, and welcome you to email us with suggestions, comments and feedback at [inspirestudentjournal@gmail.com](mailto:inspirestudentjournal@gmail.com).

Best wishes,

**INSPIRE Student Health Sciences Research Journal Editorial Team**

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# High rates of tooth extractions in children due to caries: The do's and don'ts

By Hassan Adnan

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**On the 11th of January 2017, the Local Government Association (LGA) released an astonishing statement: "160 children/teenagers are having tooth extractions under general anaesthetic per day in the United Kingdom".<sup>1</sup> Sugar, poor oral hygiene and infrequent dental attendance can lead to unwanted caries. Untreated caries can lead to severe pain, erosion of the tooth and ultimately tooth loss.<sup>2</sup> The premature loss of primary teeth can reduce space in the adult dentition, leading to misaligned teeth, requiring future orthodontic treatment.<sup>3</sup>**

Caries is the progressive destruction of dental hard tissues over time, caused by acid attack due to the breakdown of sugars by oral bacteria.<sup>4</sup> Cariogenic bacteria e.g. *Streptococcus mutans* thrive in these environments, producing the lactic acid required for the demineralisation of dental tissues – eventually leading to caries and cavities.

Tooth decay is the leading cause of child hospital admission, with 28% to 39% of five to eight year-olds in the UK having obvious untreated decay in their primary teeth.<sup>5</sup> Sugary cereals, alongside fruit juice consumption, can create optimum conditions for oral bacteria to carry out the decay process; in fact, statistics show that children consume 22-29% of sugars from cereals.<sup>6</sup> In this respect, a regular and sound oral hygiene regime is vital in ensuring this is prevented. A recent study showed that infrequent brushing in primary teeth leads to a higher incidence of new carious lesions compared to adult teeth,<sup>7</sup> reinforcing the importance of oral hygiene instructions

at an early age. Nevertheless, around 40% of children do not visit the dentist regularly.<sup>8</sup> Factors including shortages of NHS dentists, phobia and lack of awareness, can contribute significantly. Early acclimatisation within the dental surgery is essential to ensure that children become accustomed to the dental setting, leading to a less anxious state.

Between 1997 and 2006, data showed there was a 66% increase in general anaesthetic (GA) extractions due to caries.<sup>9</sup> Undoubtedly, some cases indicate the use of GA, such as the need for multiple extractions or patients unwilling to use local anaesthetic. However, GA should be the absolute final option for children due to the associated risks. Local anaesthetics and conscious sedation states should be offered prior to GA. And awareness should be made of the risks associated with GA, which vary from minor to major; for example, 1 in 100,000 cases of GA can end in mortality,<sup>10</sup> Multiple appointments,

waiting lists and clinic cancellations in turn mean that children suffer with dental pain for longer.<sup>11</sup>

To address such a major public health issue, the British Dental Association has backed a government campaign to apply a sugar levy on soft drinks with the intention of encouraging consumers to think twice when purchasing.<sup>12</sup> Meanwhile, a quarter of 11- 18 year olds receive 40% of added sugars from drinks.<sup>13</sup> Low costs and promotions play a key role in the growing economy of soft drinks. By 2018, the government hopes to have this tax placed; positive news indeed for all healthcare professions.

**'Dental patients visiting A&E cost the NHS £18 million a year'**

- British Dental Association, 2017

Do's	Don'ts
Brush 2x daily for 2 minutes with a fluoride toothpaste.	Snack between meals.
Keep sugar intake to <4x daily.	Rinse mouth out after brushing.
Keep sugar intakes to meal times only.	Use a mouthwash alone / at the same time as brushing.
Visit the dentist regularly.	Give children bottled (juice/milk) just before bed time.
Take children to the dentist as soon as their first teeth erupt (average 6 months)	
Supervise children when brushing up to the age of 7 years.	

(Delivering better oral health: an evidence-based toolkit for prevention, 2014)<sup>15</sup>

Not only are patients affected but hospital admissions for decay in primary teeth have had an impact on the NHS - a record £35.6 million was spent in 2015/16 on dental extractions for individuals under the age of 18.<sup>14</sup>

Considering current financial struggles within the NHS, investments in raising awareness of dental decay, and promoting education in prevention techniques, would reduce rates, allowing NHS funds to be spent on more life-threatening conditions.

Professor Nicky Kilpatrick, a paediatric specialist at the Royal Children's Hospital, Melbourne, states **"UK universities have a responsibility to ensure that newly graduating dental care professionals not only have excellent clinical skills, but appropriate attitudes and behaviours to support vulnerable children and families in preventing dental disease."** This reiterates the importance of not only clinical skills, but communication in treatment planning according to individual needs.

**'If we are to get serious about tackling this then prevention is the key'**

- Sarah Hurley  
(Chief Dental Officer for NHS England)

Dental decay is a disease easily prevented. Immediate investigation into and change in the rate of decay and GA referral is therefore warranted. Implementing oral hygiene instructions and dietary changes early on can prevent such catastrophic dental problems, resulting in a reduced number of inappropriate referrals. In conclusion, dental professionals should be more proactive, rather than reactive. It is our role to carry out community engagement projects, provide information, and ultimately make future changes to oral health for the better.

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# Capsular contracture: the problematic post-operative complication of breast implants

By Yashna Yadkarni

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The most common post-operative complication after breast implant surgery is capsular contracture,<sup>1,2</sup> with an alarmingly high incidence rate of 15–45%.<sup>3</sup> Capsular contracture is a hardening and tightening of the breast tissue around the implant area, which can be very painful. There are four different grades of capsular contracture, known as Baker Grades. Grades III and IV are pathological and require treatment.<sup>4,5</sup> The aetiology and pathophysiology of capsular contracture is not fully understood.<sup>6</sup> However, many studies have shown a significant correlation between biofilm formation and capsular contracture,<sup>7–15</sup> so biofilms have become the prevailing culprit.<sup>16</sup> Capsular contracture is difficult to manage; currently the only treatment available is removal and replacement of the implant.<sup>6,16</sup> This can be hugely distressing for the patient as it necessitates additional surgery and its associated risks.<sup>16,17</sup> More research is therefore needed into the prevention and management of this complication.

## Background

Biofilms are polymicrobial, dynamic heterogeneous communities consisting of bacteria and fungi.<sup>18,19</sup> The formation of biofilms is a complex and multi-stage process.<sup>6</sup>

### Stage 1

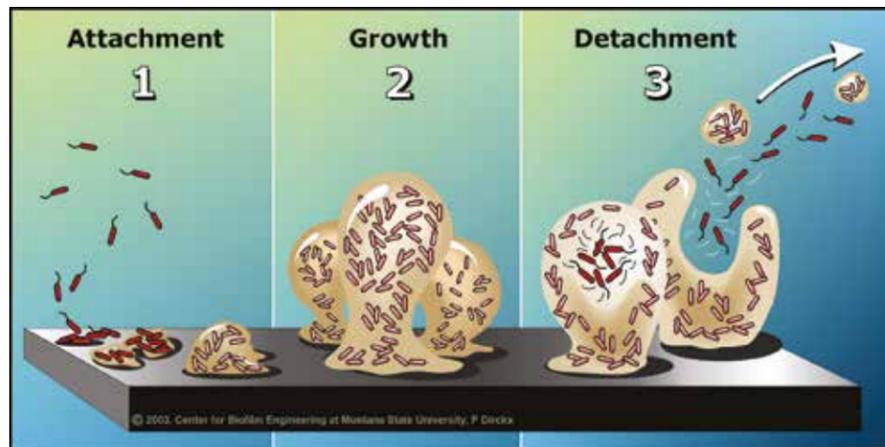
Free-floating microorganisms attach to the breast implant.<sup>6</sup> It is thought that *Propionibacterium acnes* and *Staphylococcus epidermidis* initiate biofilm formation.<sup>19</sup> Both are endogenous, non-pathogenic commensals<sup>6,17</sup> which, in the context of breast implants, become pathogenic.<sup>6</sup>

### Stage 2

The attached bacteria start to multiply, fixing themselves<sup>19,20</sup> to the implant surface. They then start to differentiate and begin quorum-sensing,<sup>19,20</sup> whereby they communicate between, and within, bacterial species to sense and react to alterations in environment to promote survival.<sup>20</sup>

## How do biofilms cause capsular contracture?

These biofilms have been shown to induce a prolonged and chronic inflammatory response as the host attempts to remove them.<sup>21,22,23</sup> This response disrupts the normal wound healing process, in particular prolonging the inflammatory and proliferative phases.<sup>6,17</sup> Due to the presence of the biofilm, many neutrophils and macrophages migrate to the site.<sup>17,19,20</sup> These cells secrete high levels of proteases and reactive oxygen species (ROS), which injure healing tissues and immune cells, thus impairing the healing process.<sup>19,20</sup> Additionally, as the inflammatory phase is extended, the macrophages secrete more chemotactic and growth factors, resulting in excessive proliferation,<sup>6,19,20</sup> thus causing disproportionate fibrosis, scarring and capsular contracture.<sup>6</sup>



### Stage 3

Once firmly fixed, the bacteria synthesise and secrete a matrix, known as extracellular polymeric substance (EPS), to surround and protect the bacterial colony.<sup>19,20</sup> Various other proteins and enzymes are also secreted to further strengthen the biofilm's attachment to the implant.<sup>19,20</sup>

## Treating and preventing capsular contracture

Breast implant texture has been implicated in capsular contracture. Many meta-analyses have established that textured implants are associated with a lower risk of clinically significant capsular contracture when compared to smooth implants.<sup>24,25,26</sup> The textured surface of the implant disrupts the contractile forces around it,<sup>27</sup> so could be a possible prophylactic strategy against capsular contracture. However, textured implants are more likely to ripple and deflate than smooth implants, and have recently been implicated in late seromas,<sup>28</sup> double capsules,<sup>28</sup> and anaplastic large-cell lymphoma.<sup>29</sup> Currently the gold standard treatment for capsular contracture is total capsulectomy, with a site change and implant exchange.<sup>6,16,17,30</sup> An open capsulectomy is an invasive procedure requiring greater dissection,<sup>16,17</sup> it is associated with increased patient discomfort,<sup>16</sup> bleeding<sup>16</sup>, and risk of pneumothorax.<sup>16</sup> A recent systematic review reported a high rate of recurrent capsular contracture after open capsulectomies.<sup>30</sup> Therefore, they are far from the ideal solution for this complication.

Multiple studies have reviewed the medical methods of treating capsular contracture. Established biofilms are notoriously difficult to treat and many studies have demonstrated that antibiotics are an ineffective treatment.<sup>31,32</sup>

### Stage 4

When fully mature, the biofilm sheds some fragments.<sup>6,19,20</sup> These may bind to different sections of the implant, thus forming new biofilm colonies.<sup>6,19,20</sup>

Current research is focused around the use of leukotriene receptor antagonists, such as Zafirlukast.<sup>17</sup> Many studies carried out in women looked at the efficacy of Zafirlukast as a treatment rather than as prophylaxis.<sup>33–37</sup> Generally, these found a reduction in the Baker grading of capsular contraction.<sup>33–37</sup> However, a more recent study looking at the long term results showed that contracture grading scores begin to increase again on cessation of treatment.<sup>38</sup> This indicates that in order to have a long term effect, patients would have to continue taking Zafirlukast; leading to a potential myriad of side effects, such as liver dysfunction.<sup>17</sup> Animal studies have found that Zafirlukast injections around textured silicone implants may be able to prevent capsular contracture from developing.<sup>37,39</sup> However, there appear to be no studies on patients given Zafirlukast as a prophylaxis,<sup>17</sup> which may be useful to look at in the future.

A flurry of new research on the use of autologous fat transfer and acellular dermal matrices has also shown encouraging results.<sup>17</sup>

Overall, the different approaches in the medical prevention and management of capsular contracture show promise. However, further randomised control trials are required to show their efficacy. In addition, these cohort studies should involve sufficient population sizes to ensure reliability of their results.

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# Chronic traumatic encephalopathy: Confronting repetitive head injury in contact sports

By Matthew Saint

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**Long-term brain damage following repetitive head injury has been found to occur in a range of contact sports, including ice hockey, association football and rugby, and wrestling. However the dependence on post-mortem examination for confirmation of diagnosis means that it is difficult to provide an accurate estimate of its prevalence. This article highlights the progress of research on detecting the accumulation of tau protein in neurofibrillary tangles in the brains of living patients, to provide a more accurate picture of this debilitating condition.**

## What is Chronic Traumatic Encephalopathy?

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease believed to manifest as a latent consequence of repetitive mild traumatic brain injury (mTBI), both concussive and subconcussive. The disease is a tauopathy - comparable to Alzheimer's disease but topographically discrete - that results in the accumulation of tau-immunoreactive inclusions throughout the cerebral cortex (Fig. 1). Associated neurofibrillary tangles are typically perivascular and focal to superficial cortical layers.<sup>1</sup> Clinically, the disease presents with deficits in attention, memory, and concentration. Inevitably, CTE progresses into overt dementia with/without parkinsonism. Additionally, individuals with CTE may experience psychiatric symptoms such as depression or anxiety, and may exhibit poor judgement, impulsivity, and lack of insight.<sup>2</sup>

The long-term neurological and neuropathological sequelae, associated with chronic mTBI, have been recognised for nearly a century in boxers. Indeed, the term 'punch-drunken' was coined as early as 1928 by Martland to describe a symptom complex which included slurred speech and a staggered, propulsive gait that had been observed in some veterans of professional boxing.<sup>3</sup> Yet it was not until 1937 that the syndrome was consolidated into a formal diagnosis. Termed 'dementia pugilistica', the name acknowledged the seemingly inextricable connection between the disease and pugilistic sports.<sup>4</sup> In the years since, emerging evidence has directly refuted the former paradigm that maintained the disease was unique to boxers, and has led to popularisation of the contemporary term 'chronic traumatic encephalopathy'.

## Diagnosis in the living?

CTE has been diagnosed and pathologically verified in the brains of ice hockey, association football and rugby players, as well as wrestlers, mixed martial artists, and American football players.<sup>5-8</sup> Rather than a new phenomenon, it seems likely that this condition has existed in veterans of these sports for years, furtively inducing distinct personality changes, depression, memory loss and progressive ataxia. It is only recently that scientists have begun to look for the disease in these athletes, and ominously, it has been discovered in disturbingly high proportions.<sup>2</sup>

However, as CTE can currently only be diagnosed post-mortem via histopathological examination, scientists are understandably hesitant about forming any meaningful conclusions about disease prevalence. Selection bias is bound to affect studies of this nature, with those athletes experiencing neurological decline in their later years

being far more likely to donate their brains to research. Identifying means to diagnose and stage CTE ante-mortem would not only allow us to accurately determine incidence and prevalence, but also to measure the efficacy of novel therapies as they emerge. With an increased understanding of the pathogenesis of CTE, we could determine whether a threshold exists, for the number and severity of brain traumas, that could be utilised to predict morbidity. We could then retire athletes before the disease manifests - or at least early in its natural course - to avoid compounding injury.

So how close are we to diagnosing the disease in living patients? Scientists have developed a number of novel positron emission tomography (PET) tracers that bind to aggregated tau in neurofibrillary tangles, which could theoretically be used to discover these pathological hallmarks in living patients with CTE.<sup>9-12</sup> However, research in this area is still very much in its infancy, and these tracers are predominantly being investigated for their efficacy in diagnosing Alzheimer disease.

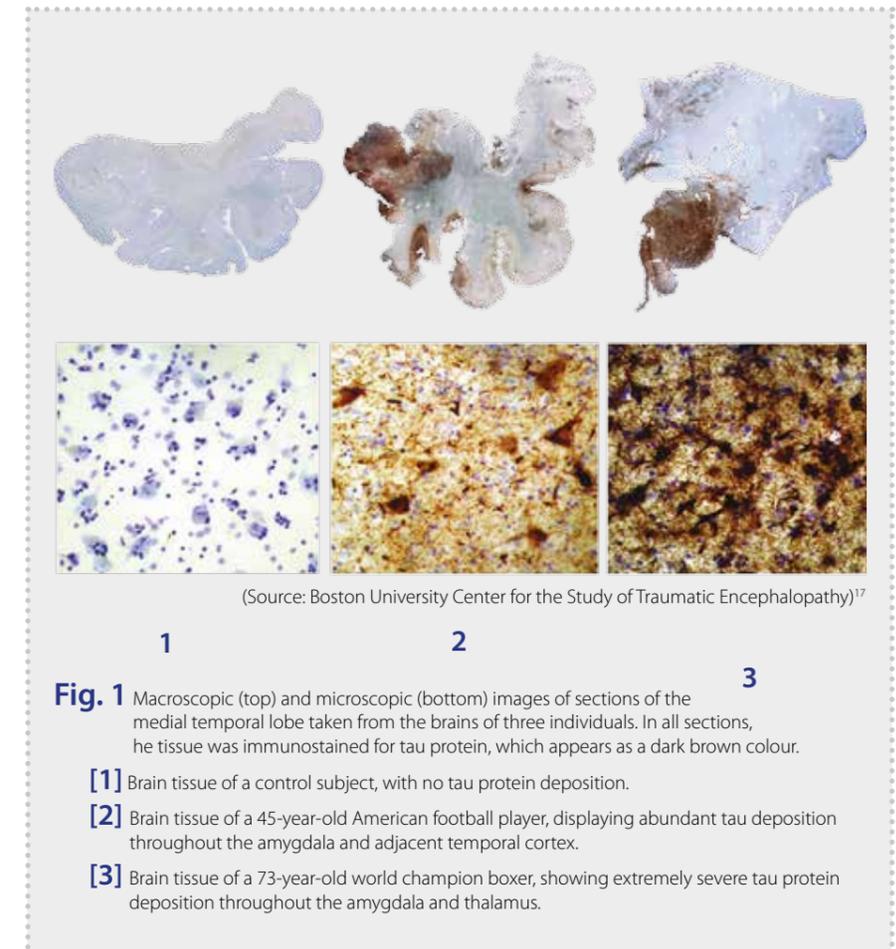
Nevertheless, a 2016 study of a retired American football player found PET tracer retention in a topographic distribution that is generally considered pathognomonic for CTE. The patient had a history of 22 recorded concussions and reported degenerative neuropsychiatric symptoms consistent with a diagnosis of CTE, which would appear to corroborate the findings.<sup>13</sup> Still, a positive tracer result has yet to be validated upon histopathological examination post-mortem, which would be a necessary condition to confirm the diagnosis and prove efficacy.

## CTE Research – A Game Changer?

Increased recognition of the long-term consequences of repetitive brain injury has led to fundamental changes to the game rules and medical suspension policy of a number of different sports. However, perhaps the most significant changes have been actioned in American football, and justifiably so: of the brains of 94 deceased former NFL players donated to the VA-BU-CLF Brain Bank, 90 of these have tested positive for CTE.<sup>14,15</sup> Clearly the burden of disease is significant here. But what about association football and rugby, both sports that have been directly associated with CTE? As of yet, aside from changes to rugby-related concussion management protocol in 2014, nothing significant has been done to minimise head injury in either of these games.<sup>16</sup> Does there need to be? It is hard to tell; without further research into the pathogenesis, prevalence and aetiology of the disease, it is difficult to justify fundamental rule changes to sports that have remained unchanged for centuries. Perhaps we must just learn to live with the fact that brain trauma is an inherent risk of any contact sport, and one that we must accept if we are to continue playing the games we love.

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**Fig. 1** Macroscopic (top) and microscopic (bottom) images of sections of the medial temporal lobe taken from the brains of three individuals. In all sections, he tissue was immunostained for tau protein, which appears as a dark brown colour.

- Brain tissue of a control subject, with no tau protein deposition.
- Brain tissue of a 45-year-old American football player, displaying abundant tau deposition throughout the amygdala and adjacent temporal cortex.
- Brain tissue of a 73-year-old world champion boxer, showing extremely severe tau protein deposition throughout the amygdala and thalamus.

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# Student-led promotion of evidence-based healthcare

By Michael Daldry

Year 1, Dentistry, Peninsula School of Medicine and Dentistry, Plymouth University

With additional contribution from Lorna Burns. Lecturer in Evidence Based Healthcare, Peninsula School of Medicine and Dentistry, Plymouth University

**NICE Evidence is a search engine designed for healthcare professionals and practitioners. It provides access to selected, authoritative evidence across all disciplines of healthcare, public health and social care. It draws upon trusted sources such as Royal Colleges, BNF, Cochrane and GOV.UK. It is freely available without requiring a login at: [www.evidence.nhs.uk](http://www.evidence.nhs.uk).**

**The NICE Evidence Student Champion Scheme is a national programme managed up by NICE. Students receive bespoke training and support to enable them to disseminate information about NICE Evidence Search to their fellow undergraduates.**

As we strive to practise evidence-based healthcare (see insert), the NICE Evidence search engine is an invaluable resource for both students and professionals. It provides quick and simple access to a vast range of information through a single search engine, which saves the time and effort of searching multiple websites and sources. Realising this, I took the opportunity to learn more about the scheme and applied to become a NICE Evidence Student Champion at Plymouth University.

Attending the workshop to become a NICE Evidence Student Champion was highly enjoyable and rewarding to learn how the scheme could further both my development and that of my fellow students. Moreover, the scheme is open to all year groups across both medical and dental undergraduate courses and this interdisciplinary aspect provided us with the opportunity to discuss and share ideas about the scope and use of the scheme across different areas of practice. The workshop provided helpful advice and guidance about facilitating teaching sessions. We were given time to practise delivering a teaching session about the uses of NICE Evidence, receive feedback, and thereby further develop our teaching and presentation skills. We were provided with a set of learning resources for our subsequent teaching which could be tailored to suit the audience. Having the opportunity to work with students from other year groups was fantastic. The highlight of the day was the practice

teaching scenarios, involving some highly entertaining role play. They showed the diversity of teaching methods that we could use for our future sessions.

Having made connection at the workshop, Student Champions are encouraged to collaborate with each other in future. I have since worked with a fellow champion and provided peer-to-peer teaching sessions, both for first year dentists and medics, with positive feedback, including "why wasn't this incorporated as a lecture into the course?".

NICE Evidence has proved to be beneficial for many students, including first year medics writing their special study unit reports. Personally, I have found it to be an invaluable tool for easy access to the BNF, especially in clinic, when time is limited and a user-friendly interface is essential. NICE Evidence is indispensable for self-directed learning, and is now my first port of call when investigating clinical topic areas.

We students need to know that the resources we use are both reliable and up-to-date. NICE Evidence brings together a range of high quality evidence including guidance, policy, systematic reviews, evidence summaries, patient information and ongoing trials. It is continually updated; much of this occurring automatically, directly from source. Students and professionals alike can therefore be confident in using the evidence to make better decisions and provide the best and most up-to-date care for their patients.

The NICE Evidence Student Champion Scheme initially focused on schools of medicine and pharmacy. More recently, however, the scheme has invited schools of dentistry, nursing and midwifery to participate. In 2016, 302 student champions from 26 schools nationwide were trained to deliver peer-to-peer teaching sessions to over 2000 fellow students. In addition, champions write a short reflective report on their experiences and are invited to the NICE London headquarters for a special event to meet, celebrate and learn about NICE. I would recommend the scheme to others who are interested in evidence-based practice and developing their teaching skills. I shall continue to use NICE Evidence and highlight its benefits to my colleagues. I can see this resource will become more and more relevant as I do increasing amounts of clinical work throughout my studies and beyond into my career.

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Evidence-based healthcare provides a process for decision making which enables us to integrate the best available evidence into our practice.<sup>1</sup> Due to the increasing volume of information that is published each year<sup>2</sup>, it is impossible for practitioners to stay abreast of every new development in their field. Evidence-based healthcare therefore takes a 'just in time' approach to using evidence, finding the best available information as and when the clinical questions arise.<sup>3</sup>) Evidence-based healthcare provides a framework for responding to a clinical query consisting of five steps:

1. Formulating an answerable question;
2. Finding the best available evidence;
3. Appraising the evidence for validity, relevance and applicability;
4. Individualising the findings with clinical expertise and patient values;
5. Evaluating one's performance.<sup>3,4</sup>

It is vital, however, that clinical decisions are based on being able to access the highest quality evidence possible, through reliable, trustworthy resources.

Lorna Burns

The image shows a screenshot of the NICE Evidence Search website. At the top, the NICE logo (National Institute for Health and Care Excellence) is displayed alongside navigation links for 'NICE Pathways', 'NICE Guidance', 'Standards and indicators', and 'Evidence services'. A 'Sign in' button is also present. Below the navigation, there are links for 'Evidence search', 'BNF', 'BNFC', 'CKS', and 'Journals and databases'. The main content area features a large blue circular graphic with the text 'Evidence search' and a search bar. Below the search bar, there is a small text box that reads: 'Make better, quicker, evidence based decisions. Evidence search provides access to selected and authoritative evidence in health, social care and public health.' The background of the page shows a group of diverse people sitting around a table, engaged in a discussion.

# Tips for Managing Anxious Patients in Dental School



How many of us are scared of the dentist?



Just over 1/2 of people in the UK report experiencing some form of dental anxiety<sup>1</sup>

Before treatment try to establish:<sup>2</sup>

- When did this anxiety begin?
- Is this related to a previous experience?
- What are you specifically concerned about?
- What do you wish to get out of this appointment?

## 'Tell, Show, Do' for Adults<sup>2</sup>

**Explain** treatment options, procedure and stop signals PRIOR to treatment

**Asking** questions should be encouraged for consent & a mutualistic approach to patient-centred treatment

**Show** using diagrams or illustrations. Describe the likely sensations (eg pressure or vibrations) and sounds they will experience<sup>3</sup>

**Do** the treatment (watch out for the previously established stop signals)

## GUIDED IMAGERY & VISUALISATION<sup>4</sup>

Guided imagery is a form of deliberate daydreaming, resulting in a focused state of relaxation.

It occurs in 3 stages:

- (1) Relaxation: slow breathing, sequential muscle contraction/relaxation
- (2) Visualisation: ask the patient to think of a pleasant, tranquil place or memory and focus on concrete details linked with all the senses: sights, colours, smells, physical sensations and sounds
- (3) Positive suggestion: the dentist can prompt visualisations by asking the patient to focus on a particular sense. It's important that the voice tone remains calm and soft

Guided imagery has been found to be effective in reducing pre-operative anxiety AND post-operative pain within the clinical environment



## DIAPHRAGMATIC BREATHING<sup>2,4</sup>

Phobias are referred to as a form of 'fight or flight' reaction and are linked with increased pain perception in the dental clinic.

Deep breaths into the abdomen inhibit the upregulation of the sympathetic nervous system & combats anxiety symptoms such as increased heart rate.

THE METHOD

- ~ Sit up straight, head upright
- ~ One hand on chest & other on abdomen
- ~ Breathe out all the air in your lungs
- ~ Breathe in evenly and for a count of 4
- ~ Exhale evenly for a count of 7

## Fear of Injections<sup>2,6,7</sup>

- "You won't be able to get me numb, I never get numb"
- "I hate big needles"
- "It is going to hurt"

Dental students have heard these fears many times on clinic. It is important to acknowledge these fears (rather than dismiss them) and again - assess if these are related to a previous bad experience.

Some useful tips:

- Provide the patient with some control** Reassure the patient that they can choose when to stop and take a break. Stop signals should be adhered to immediately.
- Combat some myths** During infiltrations remind the patient that only 1-2mm of the needle tip is used - some patients previously believe that the whole needle is used<sup>8</sup>
- Utilise topical gel** This reduces the physical sensation of mucosa-needle penetration
- Emphasise patient control** Emphasise to the patient that treatment will not occur until they are fully numb. Use testing methods such as probing the surrounding gingiva to demonstrate that the local anaesthetic has worked



## Choose your words

Our choice of language can produce the opposite effect of what we originally intended. Here are some tips to avoid this type of mistake:

### CAREFULLY<sup>8</sup>

I'm going to drill out the carious tissue to stop the pain



I'm going to clean out the stuff that has been making your tooth hurt

Don't worry, this won't hurt



Just relax in the chair, all you will feel is a little pressure

Take a painkiller later if you feel pain from the extraction



Take a painkiller before the numb feeling wears off. This will ensure maximum comfort



Yasmin Zeina  
Year 3 Dentistry, University of Bristol

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# The Future of Anterior Cruciate Ligament (ACL) Repair: The Bridge-Enhanced ACL Repair (BEAR) Procedure?

By Waheed Ahmed and Matthew Saint

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## Background

### ACL anatomy and injuries

The anterior cruciate ligament (ACL) is one of the four key ligaments of the femorotibial joint, and functions as an important internal stabiliser of the knee.<sup>1</sup> The ACL runs diagonally through the inside of the knee joint, from the medial wall of the lateral femoral condyle to just anterior of the intercondyloid eminence of the tibia. It resists rotational movement and prevents forward displacement of the tibia relative to the femur.<sup>2</sup> ACL injury is one of the most common types of knee injury, particularly amongst athletes, and accounts for around 40% of all sports injuries. Characteristically, the ACL is torn in instances of rapid non-contact deceleration, or when there is acute valgus stress resulting from rapid directional change on a fixed and planted foot.<sup>1,2</sup>

### ACL reconstruction surgery

A torn ACL causes loss of stability in the knee and a diminished range of motion. The extent of tear and the patient's history is often used to guide treatment, which may be surgical or conservative. Conservative management is typically reserved for sedentary patients because repair of the ACL through non-operative means is often incomplete; physically active patients must seek surgical treatment to restore functional strength to the ligament.<sup>3</sup> The field of ACL reconstruction surgery is continuously advancing and has evolved considerably over the past few decades.<sup>4</sup> In the 1980s, the technique tended to involve reconstruction of the anteromedial bundle using the middle third of the patellar tendon, which destroyed any remaining segment of the ACL. More modern surgery has led to the development of techniques that preserve the remnants of torn ACL.<sup>5</sup>

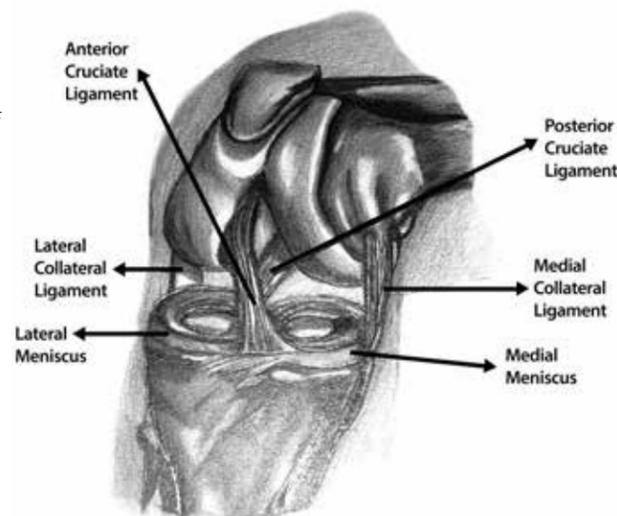
To achieve this, contemporary surgical management typically uses a substitute graft made from a tendon or ligament harvested elsewhere in the knee: most commonly the semitendinosus tendon or the patellar ligament. This procedure has proven efficacious in restoring gross stability to the knee. However, there are relatively high graft failure rates in adolescent patients,<sup>6-8</sup> and ACL reconstruction does not prevent the premature osteoarthritis regularly recorded in patients following ACL injury.<sup>9-11</sup> Clearly, there is a need for alternative solutions that circumvent these types of complications. This article focuses on the novel Bridge-Enhanced ACL Repair (BEAR) procedure as a potential alternative to the standard ACL autograft surgery.<sup>12</sup>

### The BEAR Procedure

The Bridge-Enhanced ACL Repair (BEAR) procedure uses suture repair to bridge the gap between the ends of torn ligaments and incorporates a bioactive scaffold to promote self-repair.<sup>12,13</sup> Touted as a potential breakthrough in ACL repair, this new approach has proven promising in early human trials: all BEAR recipients studied thus far have demonstrated remarkable results, reporting faster recovery time than conventional graft recipients and regaining a degree of strength and functionality comparable to that of their healthy knee.<sup>12,13</sup> In the past, surgeons have tended to avoid suturing the torn ends of the ACL together because the ligament is largely avascular and this kind of repair had a high failure rate in trials.<sup>14-16</sup> However, the bioactive scaffold used in the BEAR procedure appears to stimulate healing of the torn ACL when coupled with sutures.

The scaffold appears to incorporate elements that promote healing and tissue repair, such as a collagen-based extracellular matrix with exogenous fibroblasts. Indeed, in vitro studies have shown that fibroblasts synthesise 10-fold more collagen when cultured in this type of environment compared to regular culture plates.<sup>17</sup>

In pre-clinical animal studies, the BEAR-treated ACLs showed similar mechanical properties to the traditional patellar ligament allograft at three, six and 12 months post-operatively.<sup>18-21</sup> In addition, pigs treated with the BEAR scaffold had lower rates of complicating osteoarthritis than those treated with ACL reconstruction.<sup>22-23</sup> Furthermore, previous use of analogous scaffold was efficacious in enhancing bone regeneration following maxillary surgery.<sup>24</sup>



A recent cohort feasibility study tested the possibility of translation these results to humans.<sup>12</sup> Ten patients were assigned to traditional management involving ACL reconstruction with a hamstring autograft, while another ten underwent the novel BEAR procedure.<sup>12</sup> Outcomes were assessed three months post-operatively and included measures of post-operative pain, muscle atrophy, mobility and gross implant failure. No joint infections or signs of significant inflammation were observed in either group, nor did any patient have to return to the operating theatre for repair failure.<sup>12</sup> Furthermore, there were no differences between groups in terms of pain or incidence of joint effusion. However, hamstring strength at three months was significantly better in the BEAR cohort than the ACL-reconstruction cohort ( $p < 0.001$ ).<sup>12</sup>

Still, it is important to note that there were several limitations to this study.<sup>12</sup> Firstly, due to the small cohort size it is difficult to draw definitive conclusions about the safety of the new procedure: adverse events with a low occurrence rate may not be detected in such a small population.<sup>12</sup> Secondly, surgical outcomes were only assessed three months post-operatively. While this is long enough to detect complications relating to the bioactive scaffold (i.e. rejection of

the material by the host), it is not sufficient time for determining confidently the efficacy of the procedure or to compare this to conventional ACL reconstruction.<sup>12</sup> Finally, the trial was not double-blinded or randomised and so the investigators knew exactly which patients had received which treatment. Consequently, we should be hesitant in deciding the success of this early study.<sup>12</sup>

## Conclusion

The BEAR procedure has promise, at least in a small cohort study.<sup>12</sup> The first feasibility study in humans suggests that the BEAR scaffold is well tolerated in the synovial environment of the knee capsule, with no reports of infection or a significant inflammatory response in the three-month post-operative period. Furthermore, all ten patients who underwent the BEAR procedure had a continuous and sturdy ACL after three months and maintained a reasonable degree of knee stability.<sup>12</sup> These exciting findings suggest the BEAR technique deserves further investigation in a larger study population and for longer. Until then, however, we must be careful not to extrapolate too much from these early data. We look forward to seeing the outcome of the BEAR II trial – now fully enrolled – and whether this can demonstrate further the potential of the BEAR procedure in the surgical repair of a torn ACL.<sup>25</sup>

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# Orchestrating Orcas: The physical and mental welfare implications of a life in captivity.

By Victoria Troman

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**The orca is the largest member of the dolphin family, and its life in captivity appears to be a miserable one. There are now 61 remaining orcas in captivity around the world.<sup>1</sup> The capture process involves being taken from their family (orcas are highly social animals, travelling in large pods of up to 40 others with whom they form extremely strong bonds).<sup>2</sup> They are contained in a tank with an orca from another pod or even alone, and perform the same routine every day for the rest of their lives without family, communication or space to swim as a normal orca would. In contrast, in the wild, orcas can swim up to 100 miles per day).<sup>3</sup> Whilst one might argue that watching these creatures leap from the water and perform tricks is a magnificent sight for spectators, the welfare implications of a life in captivity could be considered unacceptable.**



Jen Helton/Shutterstock.com

One of the effects of captivity on the orca seems to be a reduction in life expectancy. The lifespan of wild orcas is remarkably long, with females living up to 80 to 100 years or more, while males can reach around 60 years of age.<sup>1</sup> Contrary to claims by marine park animal trainers about an extended lifespan in captivity, it is apparent that their lives are cut short, with the majority having died by the age of 25, most commonly from infection.<sup>1</sup>

The orca brain is large and highly developed with extensive cortical folding, which indicates a huge capacity for intelligence, emotion and memory.<sup>4</sup> The responsible brain region, the limbic system, has a greatly enlarged out-pouching in the orca brain, indicating that their ability to feel grief and emotion might even be heightened relative that of humans. There are greater numbers of spindle neurons in the brains of orcas compared to humans. These neurons are responsible for the ability to feel a spectrum of emotions, from love to extreme grief.<sup>5</sup> Indeed, one captive orca, Katina, showed extreme signs of what could be interpreted to be grief (including vocalisation and shaking) when her calf was taken away to be moved to another marine park. Additionally, a wild orca was spotted swimming with her stillborn calf on her back. It might be supposed that this is a sign of grieving and only the brain power of a highly intelligent, sentient creature would be able to process such an event, unlike animals with lesser brain power which would instinctively abandon any stillborn offspring in order to prioritise others.

The orca has evolved the ability to communicate very effectively with other members of its species. The insular cortex, the region in the brain responsible for sound processing, is more developed than the same region of the human brain.<sup>4</sup> This region, along with the operculum, is akin to the area that is responsible for speech in the human brain, which potentially explains why the orca has an impressive repertoire of vocabulary that is much more than just a range of sounds.<sup>6</sup> In addition the orca has fine-tuned its use of sonar so impeccably that it is more efficient than military sonar created by humans.<sup>7</sup> Orcas use this to calculate which prey animal is ahead of them and find its exact location. They are relentless hunters and can spend up to two hours securing each meal. In captivity, orcas can neither properly communicate nor hunt, and are therefore being deprived of the ability to perform these instinctive behaviors.

Being isolated in small enclosures and expected to repeat the same routine several times a day for the rest of their life, must surely have enormous effects on the mental welfare of the orca. In some marine parks they are kept in holding pens between shows which render them almost entirely unable to move, with the pen beginning centimetres in front of the rostrum and ending just behind the tail. They remain here for most of the day.<sup>8</sup> A frequently seen yet disregarded defect of almost all captive orcas is a collapsed dorsal fin. Seen in less than 1% of wild orcas, it is the result of living in shallow

pools and gravity exerting its effects thus causing the collapse.<sup>9</sup>

Since the release of the documentary 'Blackfish', there have been several deaths of trainers caused by captive orcas.<sup>10</sup> However there have been no records of orcas in the wild inflicting such aggression towards humans, and they often swim to the surface as they are naturally curious and keen to communicate with another species.<sup>11</sup> This only highlights the impact that being confined with such little stimulation and interaction can have.

In addition, captive orcas often have rake marks along their body walls caused by aggression from other orcas in the same tank, using their teeth to attack the non-dominant animal.<sup>12</sup>

Furthermore, captive orcas frequently have damaged or missing teeth from gnawing on the sides of their tank or on rocks lining the pool, which would appear to be a stereotypical behavior arising from the lack of mental stimulation they receive.<sup>13</sup> The first orca in captivity, Hugo, died from an aneurysm, a result of repeatedly banging his head against the tank wall.<sup>14</sup> And at a Japanese marine park, post mortem examination of a female orca showed that she had swallowed over 80kg of stones.<sup>15</sup> It would seem that these behaviours are a direct result of their unnatural habitat.

These extraordinarily intelligent creatures should not be subjected to such an extremely confined life; captivity has no benefit to their conservation. Perhaps captivity is the real killer of the killer whale.

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# Protein Shakes - What's the harm?

By Oliver Crowther

Year 4, Medicine, Bristol University

**In today's society there is huge emphasis on body image. Combine this with the highly competitive environment of medical school and what do you get? A gruelling culture of physical and mental conditioning that significant affects medical students. In addition to undertaking strenuous exercise regimes, many medical students supplement their diet with various forms of protein. However, as far as I have witnessed, there is often little awareness of potential detrimental effects of this supplementation. Given the stereotype surrounding medical students, of a person who 'has every disease in the book', I found this lack of insight surprising. Here, I aim to appraise the evidence regarding the negative effects of protein supplementation in young, otherwise healthy individuals.**

## How much protein?

When it comes to dietary supplements there is a wide variety of factors to consider:<sup>1</sup>

- Dose: Amount of amino acids per serving
- Source: Whey vs. casein
- Timing: Before or after exercise or nutrients
- Macronutrient co-ingestion: Carbohydrate, fat or protein.

## Dose

This article focuses on dose. For a non-active individual, an adequate intake of protein was 0.8-0.9g/kg/day, increasing to 1.2-1.7g/kg/day for people undergoing regular strenuous exercise.<sup>2</sup> More recent estimates of protein requirements for strength training suggest that 1.33g/kg/day is a better figure to aim for.<sup>3</sup> These guidelines suggest protein requirements are static, which is not the case. Several factors influence daily amino acid availability in the body.<sup>4</sup> Protein turnover, exogenous sources and de novo synthesis form a dynamic flux of amino acids that generates a free pool of amino acids acting as a reservoir.<sup>4</sup>

## Should you just take a massive protein load to ensure an adequate supply?

This is the norm in certain athletic groups. Dietary surveys have reported protein intake as high as 2.5-3.0g/kg/day.<sup>2</sup> So what does this do to the body? There is tight regulation over the size of the free amino acids pool. When there is excess, three compensatory mechanisms are activated:<sup>4</sup> oxidation of amino acids, ureagenesis, and gluconeogenesis.

## Potential downsides of excess protein

Through the above three mechanisms, excess protein intake potentially could have detrimental effects including autoimmune disease, bone breakdown, kidney stones, and oxidative stress.

### Autoimmune disease

Evidence that excess protein intake causes autoimmune disease is weak, and the majority of reports suggest no single macronutrient to have a role in autoimmunity.<sup>5</sup>

Only one systematic review has shown any evidence that excess protein predisposes to inflammatory bowel disease, suggesting limited reliability.<sup>6</sup> In addition, rheumatoid arthritis and multiple sclerosis emerged from ecological studies as diseases associated with a protein-heavy diet. However, this has not been supported by the more reliable case-control studies.<sup>7</sup>

### Bone breakdown

A biochemical model suggests a diet high in protein reduces blood pH.<sup>8</sup> This increase in H<sup>+</sup> ions is counteracted via renal hydrogen and calcium excretion.<sup>8</sup> Hypercalciuria stimulates release of parathyroid hormone, which acts to resorb bone and increase calcium concentration.<sup>8</sup> However, this model has been widely refuted and the opposite effect of protein is now upheld. Via activation of insulin-like growth factor-1, protein excess mediates anabolic effects on bone growth.<sup>2,9,10,11</sup>

### Kidney stones

The standard mantra of NHS guidance for patients with kidney stones still includes a low-protein diet, highlighting a link between the two.<sup>12,13</sup> There is a lot of research to support this<sup>14,15</sup> including a study showing that the consumption of excess animal protein led to an increase in serum uric acid (a cause of kidney stones) in otherwise healthy subjects.<sup>16</sup>

### Oxidative stress

In theory, oxidation of excess amino acids could increase reactive oxygen species, which cause structural changes in DNA, RNA and proteins.<sup>17</sup> Deminice et al. and Gurgun et al. have demonstrated an increase in oxidative stress and hepatic damage in response to excess protein intake in rat models.<sup>17,18</sup> However, without similar evidence in humans, no strong conclusions can be made.

## The benefits

There is overwhelming evidence regarding the benefits of whey protein supplementation, including in terms of muscle mass and strength.<sup>1,2,19</sup> Furthermore, collective scientific opinion agrees that it is advantageous to cardiovascular health,<sup>20</sup> through its insulinotropic and pro-metabolic effects.<sup>21,22,23</sup> More relevant to a medical career, protein can improve tissue repair, recovery from surgery and ulcer and burns healing.<sup>24</sup>

## Conclusions

The only potential detrimental effect of excess protein intake that is supported by evidence is the formation of kidney stones. The previously touted risks to bone health and autoimmune disease are now widely refuted. Studies on animal models suggest a link to oxidative stress, which until are confirmed in human studies, have little validity. Compared to the overwhelming evidence supporting the multiple benefits of a protein-supplemented diet, the choice seems to be an easy one.

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# University of Bristol One Health Society conference

By Isobel Wickstead

Year 3, Veterinary medicine, Bristol University

**The Bristol University third annual One Health Conference invited speakers with a broad spectrum of expertise to discuss how their work contributes to the 'One Health' concept.**

Dr Ed van Klink started the day emphasising the importance of communication between the medical professions, farmers and policymakers in the management of serious disease outbreaks, using The Netherlands' 2007 Q fever outbreak as an example.

Professor Michael Lee went on to talk about the key role of ruminant livestock in global food security in a world with a rapidly expanding population and an increasing demand for animal protein, emphasising the need to farm livestock more sustainably.

Professor Jo Cable explored the topic of aquaculture and its growing role in food security and health, whilst Professor Joe Brownlie explained his role as an expert on new and emerging veterinary diseases, and the advice he provides to different industries on their control and management.

Dr David Grant started his talk with an animation of the US Airways Flight 1549 crash-landing on the Hudson River in 2009, providing a great example of the importance of clear communication between different roles within the workplace and how this can improve patient safety and health care quality within the medical sector.

## Acknowledgements

The One Health Committee would like to thank INSPIRE for sponsoring the 2017 One Health Conference. Without their support the event would not have been possible.



Dr Gladys Kalema-Zikusoka gave a very thought-provoking talk identifying that healthcare, wildlife conservation, people's livelihoods and poverty in remote communities in Uganda are very interrelated, and that the veterinarian's role is much more than just animal medicine and welfare.

Anthony Jones from Google provided us with some mind-blowing facts about online data, how people use the internet and the problems arising from free access to online information, which may have an impact on vets, doctors and dentists in the future.

Dr Peter Kertesz, a practising dental surgeon involved in the care of zoo animals worldwide, closed the day with lots of footage of his (very variably sized!) patients, and discussed the practicalities and difficulties associated with his work.

Thank you to everyone who contributed to such a wide-ranging and interesting event, and to all those who attended. We look forward to seeing everyone at next year's conference!

# British Small Animal Veterinary Association Congress 2017

By Rachel Dalton

Year 5, Veterinary medicine, Bristol University



This year's British Small Animal Veterinary Association (BSAVA) Congress<sup>1</sup> began on a high with Bristol Vet School's very own Jacob Neeves giving a clinical presentation on a neuroscience theme, warming up our brains for the rest of the week of lectures and practical sessions. Lecture streams varied each day, with the endocrine talks proving particularly interesting. The BSAVA student stream was extremely helpful, and included tips ranging from how to manage emergency cases and how to deal with exotic animals, to reassuring students on making the transition to practice. I came away feeling a lot more confident about tackling my first budgie that comes through the door! No conference would be complete without exhibition stalls with information on veterinary jobs and products, and, of course, free pens on offer! The free water-bottles and cupcakes celebrating 60 years of BSAVA were a highlight, and it was also a great opportunity to talk with lots of vets about how to make a successful transition from student to practice.

The practical sessions were incredibly useful, and I wholeheartedly recommend them to anyone attending next year. Learning the basic steps of an ophthalmic examination with no time pressure was such a pleasure and reminded me what a great feeling it is to finish the day knowing you've achieved something.

Finally, one of the best things about BSAVA is catching up with old friends; there was such a buzz with so many vets in one venue ready to soak up the knowledge on offer. It was a great experience getting to know better the profession I am about to join, and very exciting to find out about so many new things.

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<http://www.bsavacongress.com/>

# Introduction to Cardiothoracic Surgery Conference 2016

By Waheed Ahmed  
Year X, Course X, X University

**Cardiothoracic surgery is often described as the ‘cream’ of the medical profession and attracts the UK’s top range of physicians and surgeons, according to Professor Heymann Luckraz, consultant cardiothoracic surgeon, who gave the first presentation at the Cardiothoracic Surgery Conference 2016.**



Samrith Na Lumpoon/Shutterstock.com

Cardiothoracic surgery is the field of medicine involved in the surgical treatment of organs inside the thorax, namely the lungs and the heart. Surgeons specialising in this area have a substantial impact on patient outcomes. Lung cancer is the leading cause of cancer death in the western world and is often associated with poor prognosis. However, with early detection, surgical intervention is viable and can provide stage IA non-small cell lung cancer patients with a 5-year survival rate of over 60%.<sup>1</sup> Furthermore, organ failure therapy is particularly helpful in managing heart disease and restoring patient independence and dignity.

Professor Luckraz described how cardiothoracic surgery is constantly

advancing. With the increasingly widespread use of minimally invasive approaches in surgical intervention, such as percutaneous aortic valve replacement, video-assisted thoracoscopy surgery (VATS), and endoscopic vessel harvesting for coronary artery bypass graft (CABG), patient outcomes are continuously improving.

Exciting new technology such as VATS makes clean and thorough surgical dissection possible. However, in many cases open surgery is still necessary. This is especially true in chemo-radiotherapy patients where anatomical structures have been damaged, leaving tissue difficult to differentiate.

Consultant thoracic surgeon Mr Mohammad Hewari talked about outcomes after VATS, where patients experience less post-operative pain and retain the ability to cough, reducing infection rates. Furthermore, an overall reduced blood loss curtails post-operative complications and mortality rates.

Mr Abdel-Aziz discussed the superiority of CABG compared to stent angioplasty for coronary heart disease, as demonstrated by the five-year SYNTAX study.<sup>2</sup> He also discussed different conduits for CABG procedures. These typically include the radial artery, left internal mammary artery, right gastroepiploic artery, inferior epigastric artery and the saphenous vein. With endoscopic vessel harvesting these can be removed with minimal scarring and reduced infection.

Continuing the topic of bypass surgery, consultant cardiothoracic surgeon Professor Mishra discussed coronary artery anastomosis for ameliorating angina and myocardial infarction by restoring vital

blood supply to cardiomyocytes. However, great prudence is required to facilitate optimal geometrical positioning and vessel symmetry, for good flow and haemostasis.

The conference was aimed at junior doctors and provided a superb opportunity for hands-on, simulated learning. There were several wet lab sessions throughout the day, which enhanced basic cardiothoracic surgical skills and tested our manual dexterity.

In the wet lab, we implemented our new understanding of minimally invasive cardiothoracic surgery by using VATS to carry out lung resections. We also performed chest drain insertions in sheep carcasses. Under the tutelage of Professor Mishra, we learnt how to carry out a CABG procedure on pig hearts and aortic valve replacement using a hybrid prosthesis made from bovine pericardium and pig tissue.

To summarise, it was a very informative, hands-on and thought-provoking day. As an aspiring surgeon, being able to gain an early insight into the field of cardiothoracic surgery from top consultants has been both inspiring and invaluable.

Read more about the conference here: <http://bit.ly/2w75xfX>

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# Dr Alex Harding

Exeter-based GP and Sub-Dean at the University of Exeter Medical School

By Theodore Howard  
Year 4 Medicine, University of Exeter Medical School

## “Think of Nike – Just Do It!”

### What made you decide to do your PhD?

The honest answer is quite a few things:

- 1) I thought it would focus my interest on one area.
- 2) When you spend time with people who have doctorates, you begin to realise a change in the way you think – in how you perform critical analyses, express ideas, and present them on paper. It gives you a pretty impressive skillset.
- 3) There is no doubt that a doctorate is a qualification that opens doors.



### Where does your interest in clinical education stem from?

I enjoy interactive teaching, talking and discovering things about the practice. The experiences I had whilst at medical school were absolutely rubbish. I couldn't believe that education could be delivered that badly. We spent time hanging around wards being ignored, or being rude to, and experienced lectures which were, quite frankly, boring. I had looked at medical school as the absolute pinnacle of aspiration, thinking it would deliver more than that. I was very disappointed. Surely there were better ways of delivering knowledge. As I became more involved with medical education, one of the things that motivated me was the expense. We are very lucky to have the resources we do. Therefore, we all have a duty to make sure public money is spent wisely.

### Could you summarise what you discovered during your recent thesis?

In a nutshell, the thesis looks at how clinical students learn on the wards.

I was specifically interested in what happened following the ward rounds – when the consultant sends students to see patients.

They are suddenly thinking, “Oh God, what do I do now?” How do you get from that position to learning something from a patient?

I found that to facilitate clinical learning in an environment like a hospital, you have to have a whole host of factors singing together. And these harmonise to what they call ‘socio-material networks.’

Students must present themselves in a certain way: how they dress, speak and even carry themselves may very well determine whether they find themselves exposed to the patient contact that is crucial for effective learning. These social factors intermingle with material elements such as ensuring the students have cards that will allow access into the necessary wards.

One of the principal findings was that, in order to form a network, an inordinate amount of time and energy is required.

### How do you hope your thesis will change the medical curriculum?

One of the points of interest is to make a more engaging curriculum by designing a learning programme to help modern medical students.

Initially, students do not know the consultants, nurses, or (most importantly) the junior doctors. So we have put into place changes that allow better and easier communication between students and junior doctors.

Moreover, particular attention should be drawn to the lack of teaching about the technical elements of a hospital. My research showed that students did not know how to operate bleep systems, door access codes or even where to access toilets. These simple things can really impinge on their learning.

The research also has theoretical outcomes. The dominant idea is that medical students learn through becoming part of a community of practice, as a member of a team, but I do not think this occurs. In fact, it is quite the reverse and they are often excluded. If you look at the way medical students learn in the 21st century: they learn through short-lived but very intense learning networks where a number of things come together and fire off.

Methodologically, I have stressed the importance of actually observing medical student learning rather than interpreting what they say, as these can be very different. For the first time, I was applying ‘Actor-Network theory’ to interpret observations of medical student learning.



### What were the highs and lows during your thesis?

I have never been so intellectually stretched - it was fascinating!

However, writing up the thesis was a massive task that took more time than I thought it would. I had to work at weekends and late at night, which had an impact on my family and social life.

And understanding the level of precision and clarity needed, as well as the need to repeatedly revise what you have written, were quite tough aspects of it.

### What is your advice for students interested in research?

Think of the Nike advert – Just Do It! Really. Just get yourself stuck in and start something!

# Dr Alexa Wonnacott

Clinical Research Fellow at the Nephrology Institute

By Grace Hosking

Year 3, Medicine, Cardiff University

“You must be ready for knockbacks and prepared to get up and try again.”

### How did you initially get involved in research?

I initially got into research as an undergraduate by doing the Erasmus scheme – mainly because I thought it would look good on my CV. I was really lucky because I got placed in a fantastic unit with a Professor researching the genetics of neurodegenerative disease. I spent three months there and loved every minute. We had a publication from that work – I did the main write up – then presented it in Gothenburg. Not only did I enjoy the lab side of things, I also really liked the writing and sense of accomplishment. From that point, I knew that I wanted to do more research in my career. I wasn’t quite sure how to go about it, so in my foundation years looked for every audit opportunity to get involved in. Again, I was lucky as my registrars were interested in research and I was able to contribute to a few projects. In 2010, I applied for a Welsh Clinical Academic Training Fellowship (WCAT) and because I’d shown interest from such an early stage, my CV was quite competitive.



### Was it that supervisor during your Erasmus who initially inspired you?

Yes definitely, he was fantastic and remains an inspiration now. The other mentor I had was Dr Soma Meran, my registrar when I did a renal rotation as an F2. She had just finished a PhD and was doing a fellowship, so I saw how she had got onto the career track, which wasn’t quite as well defined then as it is now. So it was partly the good fortune of meeting the right people, combined with that underlying drive to do research.

## From INSPIRE to SciNexus: an ongoing journey of medicine and research

By Rachel Dbeis

Year 5 Medicine, Plymouth University Peninsula Schools of Medicine and Dentistry

### So how did you become a clinical research fellow?

The WCAT is a clinical academic training fellowship. Instead of applying for a normal registrar job in nephrology, I applied for an academic registrar job. I do my training like everybody else but integrated within the scheme is a three-year PhD, and at all times, during my clinical training, I do academic work on the side. The WCAT is becoming more and more competitive because it's so well structured and protected.

### What is your current research about?

My PhD is about microRNA regulation of insulin sensitivity of the podocyte, to see if there are new therapeutic options for treating diabetic nephropathy. As a clinician seeing countless patients with diabetic nephropathy, you feel completely helpless, basically waiting for them to develop end stage renal failure, so this was the condition that I wanted to investigate further.

### How do you balance clinical work alongside research?

It's very tricky and any clinical academic will say it feels like constantly spinning plates. It's also the teaching aspect that you're expected to take on. It's difficult but if you are ruthlessly efficient with your time it certainly can be done. I work part time four days a week and have two children so organization is something I've become very good at!

### In nephrology, what do you think is the most exciting research happening at the moment?

We focus on microRNAs, very small sections of non-coding RNA that affect up to 60% of coding genes. We didn't know they existed 20 years ago. Now everybody wants to know whether these could be new therapeutic targets, not just in diabetes but for treatment of other conditions such as AKI and in managing transplantation as well.

### What are the most valuable skills learnt by doing research?

I think the skills that are most transferable from research to medicine definitely include efficient time management and self-motivation. The extras you gain from being a researcher are probably analytical thought, problem solving and innovation.

### What advice would you give to a student thinking about pursuing a research career?

Get involved as early as you can! Seek opportunities for experience to make sure you are interested in research because it is a big commitment, especially as a clinical academic. Once you've got the bug, go for it; you just need to persevere. There will be hurdles and some rejections and failures along the way, especially in getting funding. You must be ready for knockbacks and prepared to get up and try again. As medics that is something we aren't that good at.



Academic medicine can be broadly divided into research, teaching and leadership.<sup>1</sup> Yet, for many medical students, it remains full of uncertainties: what is it, why get involved, and how to go about it?

As someone who is familiar with these questions, I am hoping to shed some light on the opportunities available for research as a medical student through a personal account of my experience.

My journey in academic medicine started during my first year of medical school, when my colleagues and I formed a research society aimed at encouraging medical students to engage in academic medicine. Student societies are a great way to express interest in specific branches of medicine, connect with people and open up doors to invaluable opportunities. It was through the society that I was introduced to the INSPIRE initiative,<sup>2</sup> which helped me undertake a laboratory summer studentship in neuroscience. This exposure to scientific research was essential to understanding what goes on behind the scenes in medicine and science.

Since its creation, the INSPIRE initiative has continuously provided students with wonderful opportunities, from presenting at national conferences to participating in the events of the Academy of Medical Sciences. Through INSPIRE I worked with the National Student Association of Medical Research (NSAMR),<sup>3</sup> a great collaboration that supports research amongst medical students through their academic societies. NSAMR advertises its activities and available opportunities through societies, universities and social media.

After my fourth year of medicine I intercalated in a MSc by Research at the University of Exeter. This offered me a new perspective on research as a career. It taught me about its challenges and difficulties, but also about the flexibility it offers, the wonderful teams one can work with, the excitement of discovering something new, whether small or large, and the endless possibilities for progression.

Recently, I was accepted on the Academic Foundation programme at the Royal Devon & Exeter Hospital, where I'm hoping my relationship with research will continue. The programme is another magnificent way to combine clinical medicine and academia. It gives doctors protected time to pursue research interests without delaying their clinical training.<sup>4</sup> It also provides an excellent opportunity to 'try out' an academic career and develop key skills that will be useful in all areas of medicine and life.<sup>5</sup>

Many questions and fears could have prevented me from engaging in research:

- Am I good enough?
- I don't have any experience so I probably shouldn't ask to be involved.
- How do I get involved?
- What even is research?

Luckily, the people I have already met have helped me face my fears and find answers to my questions. I encourage students to engage with these organisations and others actively working to promote academic medicine and support medical students.

I also recognise that knowing where to start can be challenging. So in an effort to continue engaging in academic medicine on a wider level, and to provide students with easier access to opportunities, SciNexus was born.

## What is SciNexus?

SciNexus is an online platform, created in partnership with my colleague Arissa Tang, to encourage research and collaboration within the medical community.

It is a website that allows promotion of research, audits and quality improvement projects between doctors, medical students, academics, healthcare providers and NHS staff.

This user-friendly platform will allow people to create profiles, publish projects, recruit collaborators, share quality improvement ideas and promote research and leadership within the healthcare world.

## What do I get out of it as a medical student?

Available opportunities will range from small local audits to national collaborations. Students with no previous experience are able to participate, learn and gain experience. Projects may lead to local or national oral presentations, poster or abstract presentations, research publications and even higher degrees such as MSc or PhD. This will help students gain exposure to different ways of engaging in academic medicine and research environments, understand evidence-based medicine and enhance their experience and CV. It will also give students, doctors and healthcare professionals the ability to connect, collaborate and advance.

## How do I get involved?

Joining SciNexus is simple. Use your name and email to sign up at [www.scinexus.co.uk](http://www.scinexus.co.uk). Then create your profile, which is a snapshot of yourself, your interests and achievements you want to highlight. Post ideas for collaborations and projects, or search for opportunities by hospital, geographical location, specialty and type of research. Once you find a project you would like to get involved in, simply apply! Others will be able to see your profile and arrange to collaborate with you if your application is successful.

**Finally, my advice to anyone considering research is: do it. Research is a very rewarding experience that opens doors and opportunities you never thought possible. Whichever way you choose to be involved, the biggest barrier is making that first step — that many have taken to never look back again.**



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# Planning a research elective: possibilities and pitfalls

By Anna Kathryn Taylor

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**The elective period at the end of medical school is an incredible opportunity to work almost anywhere in the world, doing almost any kind of medicine. The possibilities can seem innumerable, and it is certainly challenging narrowing down what you want to do. Focusing on research can be an extremely fulfilling elective choice, and may lead to a publication or conference presentation, as well as enabling you to make connections with academics with whom you may continue to collaborate over the course of your career.**

## What did I do, and why?

For my elective, I decided to combine clinical experience with research, for three reasons. First, I have been involved in research for the last four years, so a two-month period where I could focus on a project of my own design was an opportunity I could not pass up. Secondly, I wanted to gain clinical experience in psychiatry and general practice, the specialties I am most likely to pursue after graduation. I hoped that doing both clinical work and research would enable me to experience what a clinical academic career is actually like, and how I might balance the challenges and pressures of each. Lastly, I wanted to gain insight into how health policy affects healthcare provision, and I felt that both the clinical and research facets of my elective could help with this.

I met my elective supervisor, an academic from the University of Melbourne, at a primary care conference in July 2015, where she presented some of her team's research into depression. Depression is a key research interest of mine, along with suicide, domestic violence, medically unexplained symptoms, and health policy. Her work looked fascinating and I was keen to learn more. I talked to her briefly after the session and followed up by email after the conference to ask about opportunities for a 2017 elective.

We started to develop ideas for a project through discussion by Skype and email.

I wanted to enhance my expertise in qualitative methodology, which I had used in other projects, but we had to ensure it would be possible to finish the data collection while I was in Melbourne.

We finalized the project design in early 2017, including gaining ethical approval. Prior to leaving the UK I conducted a literature review that informed the development of the topic guide I would use for interviews, and provided background or my research publication. This ensured that I could spend the maximum amount of time recruiting participants, interviewing, and analyzing data.

## The project: subthreshold depression

My project aimed to explore how patients with subthreshold depression managed their mood, and how they wanted their GPs to support them. Subthreshold depression is common, with prevalence in primary care of up to 9.9%.<sup>1-3</sup> It also has a significant functional impact.<sup>4,5</sup> Although there is a high spontaneous recovery rate, it is a strong predictor of major depression.<sup>6-8</sup> There is currently little in the literature about how best to treat this population. The majority recover, so active intervention may risk overmedicalisation of natural fluctuations in mood. However, many people will develop depression so this group cannot be ignored. It is also important to consider what patients themselves think about treatment, as

this affects their concordance with management strategies and their help-seeking behaviour.

I conducted interviews with fourteen participants, covering: management of mood, perceptions of self-help as treatment, and the role of the GP. I transcribed these interviews verbatim, analysed the data, and summarised it in a framework, which helped me develop the emerging themes. In my remaining time in Melbourne I focused on refining the analysis and drafting the publication. I also participated in research seminars and programme meetings, presenting my work to the rest of the team, and had clinical time with a number of psychiatrists and GPs. Since my elective, I have been working with my supervisors to finish the publication and prepare it for submission to a peer-reviewed journal. I have also identified several conferences at which to present my findings over the next year.

Although I focused heavily on gaining experience in research, it is certainly possible to spend a greater proportion of elective time in clinical practice. The nature of an elective is that you can identify your priorities and organise your time accordingly.

For the rest of this article, I will summarize the opportunities available in research and some of the challenges you may face, and offer some learning points for planning your own elective.

## What kind of research can you do?

The short answer is: almost anything! No matter what your interests are, there is likely to be a project suitable. Research includes an array of different methodologies, such as quantitative, qualitative, mixed methods, and systematic reviews. Quantitative methods may be utilised in laboratory-based research, or in epidemiological and statistical research. Qualitative methods usually involve conducting interviews or focus groups to explore participants' feelings or experiences. Mixed methods research combines both quantitative and qualitative methodologies. Systematic reviews identify and summarise the known evidence base for a specific research question. Audit or quality improvement projects also provide some experience of conducting research.<sup>9</sup>

There are, of course, opportunities and obstacles with any research methodology, depending on your personality and project. Some people prefer a concrete set of tasks or enjoy carrying out experiments, so a quantitative project focusing on laboratory work or epidemiology (the so-called 'hard sciences') may suit them. Others may prefer to spend the majority of their time talking to patients or exploring the nuances and meaning of language, so a qualitative project may be more suitable.

Carrying out secondary statistical analysis of data is not always reliant on collecting new information, so can be a fairly flexible project that is easy to complete if you know how to use the statistical software. However, if you also need to collect data (for example, by identifying facts from patient notes), you may be limited by your ability to gain access.

Qualitative research can be extremely rewarding in terms of taking a holistic approach to the participant, and may confer the additional benefit of helping you to develop your communication skills. However, it can stall if recruitment proves difficult or unpredictable.

You may also need to work slightly more unsociable hours (e.g. evenings and weekends) which are often when people are available for interview. On the other hand, if the transcripts are already available, secondary qualitative analysis is extremely flexible!

It is therefore vital to think realistically about how much you will be able to complete in your elective time, and plan accordingly. Completing an entire project from start to finish within two months is unlikely unless you are experienced in research already, or willing to do a lot of preparation (such as organising ethical approval or writing the research protocol) before you start the practical aspects at your destination.

## Potential challenges, and how to overcome them

Before finalising your research elective, consider:

- How much time to devote to research. If your main elective goals are research-oriented (e.g. to learn a new technique or method of analysis, or achieve a publication), you may choose to spend more time on your research and less time in a clinical environment. On the other hand, if you would prefer to spend more time doing clinical work you may need to identify a smaller or more flexible project to ensure you will complete it.
- Inexperience can make people nervous about committing to a research project. Don't let this put you off; everyone has to start somewhere! The important thing is to be enthusiastic and committed, and ensure that your supervisor knows what support you may need. You will likely learn very quickly, which will give you confidence to take on other research in the future. With any time-limited project, especially if you lack experience, it is crucial not to overestimate what you can achieve. It is much better to finish a smaller project than never finish a larger one, as you may still be able to present or publish the work.

Finally, you may already have taken into account the possibility of a language barrier when deciding on your preferred part of the world. However, this can be particularly important with a research elective, as communication with your team (and potentially your research participants) must be clear and accurate in order to be successful.



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## Is there funding available?

Yes! I received elective bursaries from the Royal College of Psychiatrists (through a Pathfinder Fellowship<sup>10</sup> awarded in 2015), from INSPIRE,<sup>11</sup> and from the Faculty of Health Sciences.

Other funding sources include Royal Colleges, e.g. the Royal College of General Practitioners, Royal College of Radiologists, and Royal College of Surgeons. Medical societies and organisations may also offer bursaries, such as the British Society of Dermatologists, the Renal Association, the Institute of Medical Ethics, and the Royal Society of Medicine. There are also charities, like the Medical Women's Federation and the British Medical and Dental Students' Trust, that offer elective bursaries.

## Other things to think about:

- Before you begin: Work out what you want to get out of your elective. Where do you want to work? What are you interested in? How much time do you want to spend doing research? Do you want to develop your own project or contribute to an existing one? Are you hoping for a publication or presentation about your findings?
- Finding a supervisor: There are a number of ways to do this. Meeting your supervisor in person, at a conference or another research networking event, is a good way to establish contact. However, this is unusual unless you start thinking about your elective early and attend conferences related to your interests. An easier way would be to ask a local clinician or academic working in your area of interest if they know anyone conducting research in countries you'd like to work in. They may then be able to introduce you to an international colleague, and vouch for you. Lastly, you can directly contact a potential supervisor by looking researchers up on university websites and emailing them.
- Finding bursaries: It is important to start early. Some bursaries require you to submit an application perhaps months, or more than a year, in advance of commencing your elective, so the sooner you start searching the better; you don't want to inadvertently miss the deadline or not have enough time to finish the application!

Whether you've done research before, or are keen to dip your toe in the academic waters for the first time, the elective period is a fantastic opportunity to participate in research that could both positively affect patients and benefit your career for many years to come.

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# The use of celastrol in the fight against obesity

By Julia Cheong

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Diet-induced obesity constitutes a global burden that contributes to numerous debilitating chronic diseases such as type 2 diabetes mellitus. The 'satiety hormone' leptin plays an important role in helping to regulate normal body weight, but in obese individuals, high levels of circulating leptin appear to be ineffective at reducing appetite or weight. In the search for a new therapeutic approach, recent attention has turned to celastrol, a phytochemical with newly found 'anti-obesity' properties.

## Introduction

Obesity now affects 27% of adults in England, and the yearly cost of treating health complications secondary to obesity, including type 2 diabetes mellitus, has escalated to £6 billion.<sup>1</sup>

Leptin, commonly known as the 'satiety hormone', is a polypeptide encoded by the adipocyte-specific gene *ob* (obese). Leptin actively participates in homeostatic processes such as immunity, inflammation and, most importantly, maintenance of normal body weight.<sup>2</sup>

In the brain, leptin acts as a signal for adiposity and its levels vary according to the amount of fat present in an organism. Leptin suppresses appetite and the intake of food through its action on the hypothalamus.<sup>3</sup>

The majority of obese individuals have highly elevated circulating leptin levels due to the presence of considerable fat mass.

## Thunder God Vine: The Holy Grail of weight loss?

Celastrol (C29H38O4) is an active pentacyclic triterpenoid compound obtained from the root of the Thunder God vine (*Tripterygium wilfordii*), a shrub best known for its anti-inflammatory and immunosuppressive properties.<sup>7</sup>

Investigations have also confirmed anti-cancer properties of celastrol through its apoptotic effect on tumour cells, inhibiting proliferation of a wide range of tumour cell lines in multiple myeloma and non-small cell lung carcinoma.<sup>8</sup>

A 2015 study demonstrated that celastrol acts as a therapeutic agent in the treatment of obesity.<sup>9</sup> Four types of mice were used: diet-induced obese (DIO) mice, normal lean mice, leptin-deficient (*ob/ob*) mice and leptin receptor-deficient (*db/db*) mice. The injection

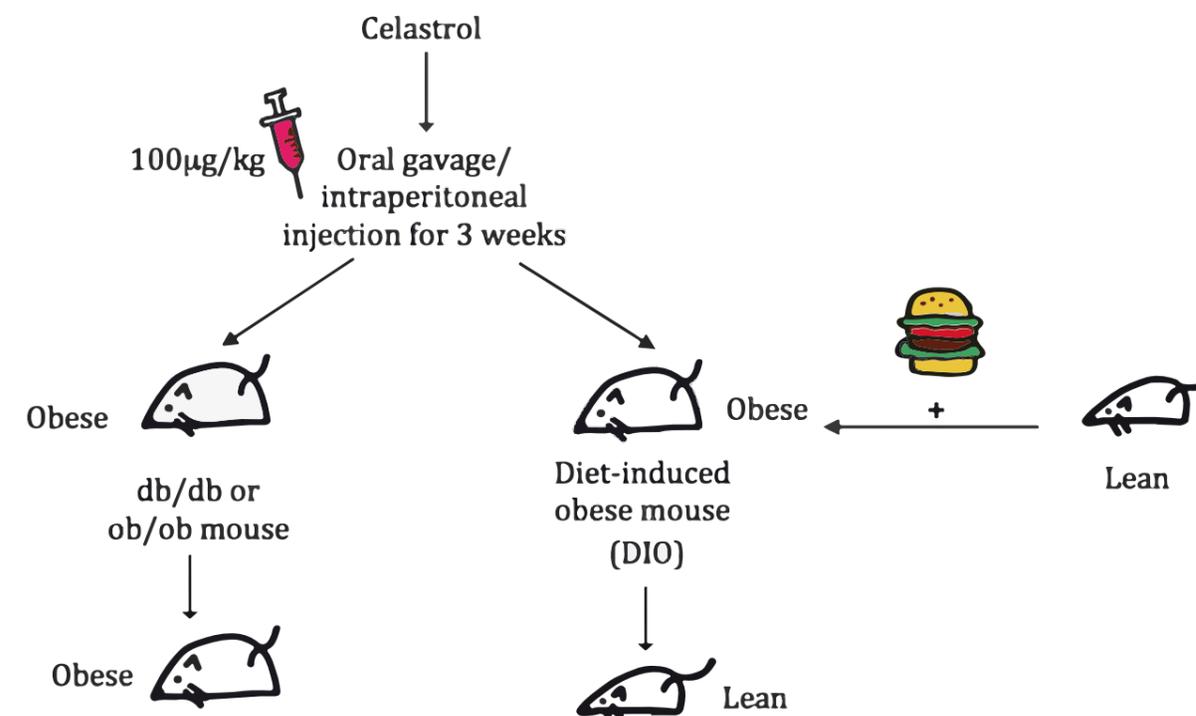
of celastrol (100 µg/kg) for 3 weeks resulted in significant weight loss of about 25.5% (mostly from fat) in DIO mice only. No weight loss was observed in lean, *ob/ob* or *db/db* mice, suggesting that celastrol improves leptin sensitivity, possibly through its action on the hypothalamic circuitry.<sup>9</sup>

Diet-induced obesity is also considered as a state of chronic inflammation and is strongly associated with metabolic conditions such as insulin resistance and type 2 diabetes mellitus.<sup>5</sup> A high-fat diet (HFD) potentially increases synthesis of reactive oxygen species, which in turn result in oxidative stress and injury through oxidation of low-density lipoprotein (LDL), ultimately promoting obesity.<sup>6</sup>

Several recent studies have explored the potential of antioxidants and anti-inflammatory compounds to suppress obesity. One promising example is the experimental use of celastrol as a future 'anti-obesity' drug.

of celastrol resulted in significant weight loss of about 25.5% (mostly from fat) in DIO mice only. No weight loss was observed in lean, *ob/ob* or *db/db* mice, suggesting that celastrol improves leptin sensitivity, possibly through its action on the hypothalamic circuitry.<sup>9</sup>

Furthermore, leptin administration to lean, DIO and *ob/ob* mice pre-treated with celastrol resulted in a decrease in food intake and considerable weight loss in all three types of mice compared to their control groups. These results imply that celastrol also mediates and enhances the effects of leptin in inducing satiety (Figure 1)<sup>9</sup>



**Figure 1.** Celastrol-induced weight loss in DIO mice but not in *db/db* or *ob/ob* mice. Decreased food intake, body weight, ER stress, and increased glucose homeostasis and leptin sensitivity were observed in DIO mice treated with celastrol. However, administration of leptin to *db/db* and *ob/ob* mice pretreated with celastrol did induce weight loss.<sup>9</sup>

Further research, conducted on HFD-fed mice and regular chow-fed mice, identified the protective properties of celastrol against obesity and associated metabolic dysfunction to involve stimulation of the HSF1/PGC-1 $\alpha$  transcriptional axis.<sup>10</sup> (Chow meals are high in fibre and contain complex vegetable carbohydrates.<sup>11</sup>)

Surprisingly, while food intake was unaffected, adipose mass in both types of mice was reduced in comparison to their control groups, showing that celastrol increased energy expenditure by upregulating heat shock factor 1 (HSF1). HSF1 is a DNA-binding protein regulating energy metabolism and expenditure via the stimulation of the peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ). PGC-1 $\alpha$ , in turn, activates mitochondrial function and oxidative metabolism in fat and muscle to increase energy expenditure (Figure 2). Upregulating the HSF1/PGC-1 $\alpha$  axis can therefore help to reverse metabolic disturbance and damage caused by obesity.<sup>10,12</sup>

Lastly, a separate study performed on HFD-fed rats explored potential effects of celastrol on HFD-induced oxidative stress.<sup>13</sup> Indeed, a HFD in the long run disrupts the cholesterol pathway and increases risk of myocardial infarction. This type of diet also contributes to the formation of lipid-rich plaques on arterial endothelium through the upregulation of LDL production.<sup>14,15</sup>

Administration of celastrol considerably improved plasma high-density lipoprotein (HDL) level and lipid metabolism in the HFD-fed rats. Celastrol thus restored the cholesterol pathway, significantly decreasing the levels of reactive oxygen species. Furthermore, celastrol increased antioxidant enzyme activity, attenuating chronic HFD-induced oxidative stress and exerting its protective effect against obesity.<sup>13</sup>

Other phytochemicals from green tea, white mulberry and ginger plants, have also shown significant results in reducing body weight.<sup>16</sup> However, their exact mechanism of action on human metabolism also requires deciphering.

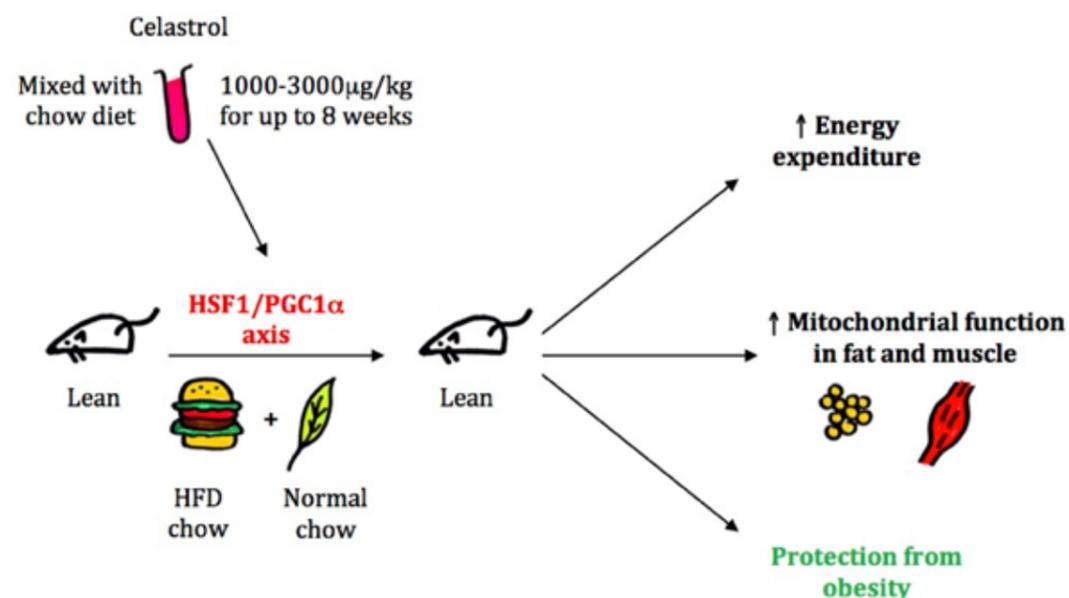


Figure 2. Fat and muscle mobilisation through the activation of the HSF1/PGC-1 $\alpha$  axis resulted in increased energy expenditure and subsequent improvement in muscle endurance.<sup>10</sup>

## Conclusion

Celastrol clearly remains a resourceful compound with powerful therapeutic and protective uses against obesity in mice. Further clinical research needs to be conducted to ensure that the phytochemical can be administered safely and effectively to humans. With up to 60% of individuals predicted to be obese by 2050,<sup>17</sup> pharmacological interventions need to be tested and implemented as soon as possible. There is hope that celastrol could give rise to a new generation of anti-obesity drugs to actively tackle society's current struggle with unhealthy weight gain.

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# Faecal Microbiota Transplantation: promising treatment for Clostridium difficile infections?

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## Abstract

With a relapse rate in excess of 30% and increased 30-day mortality rates of up to 15%, Clostridium difficile infection (CDI) is rapidly becoming a leading concern for elderly, bedridden patients. Recent research into the microbiota and pathogenesis of CDI has provided the opportunity for developing more targeted treatments. Faecal microbiota transplantation (FMT) replenishes microbial diversity, thus potentially becoming an important component of CDI management. Donor selection and route of administration may influence success rates, but with recent improvement in stool storage, this approach certainly has potential. There may, however, be intervention-related adverse effects. This article reviews FMT methodology and cure rates, and will discuss current challenges regarding logistics and other possible complications.

## Introduction

Clostridium difficile is an opportunistic toxin-producing pathogen responsible for 15%–20% of all antibiotic-associated diarrhoea cases with variable severity in hospitalised patients.<sup>1</sup> Hospital-acquired C. difficile infection (CDI) increases 30-day mortality rates by up to 15%.<sup>2</sup> Treatment with broad-spectrum antibiotics has been linked to the pathogenesis of CDI through a decrease in faecal microbiota diversity.<sup>3</sup> Current management guidelines recommend the use of metronidazole or vancomycin. However, their efficacy has been diminished due to the emergence of hypervirulent strains, such as 027.<sup>4</sup> With the limited efficacy of treatment varying from 30–80%, and over 30% of patients relapsing after initial treatment<sup>5,6</sup> there is a growing need to find a feasible cure for CDI. Faecal microbiota transplantation (FMT) is progressively becoming a viable and safe therapy for patients who suffer from recurrent CDI.

Currently, there is no universally approved methodology for donor screening, stool preparation or the means of administration, which is hindering the development of FMT as a globally available treatment. It is feasible that patients would be reconsidered for treatment following reports of a cure rate of up to 94%.<sup>7</sup> Short-term adverse effects<sup>7</sup> and numerous instances of self-administration using unprocessed stool have been reported.<sup>5</sup> This has the potential to become a dangerous practice, highlighting the need to explore the complications and to establish a universally-agreed procedure. This article will discuss the relationship between methodology, cure rates, complications and the mechanism of action, to explore whether FMT is an effective method to combat CDI.

## Methods

'Web of Science', 'Google Scholar' and 'PubMed' databases were primary search engines. Keywords included 'bacteriotherapy', 'microbiota', 'clostridium difficile', 'clostridium infection', 'faecal transplantation', and 'faecal donation'. Searches were limited to the last decade.



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## Results and discussion

### FMT Methodology and Success Rates

Most studies in this field are of poor quality, with few randomised controlled trials (RCTs), few participants and abundant methodological variations.<sup>8</sup> Nonetheless, an open-label RCT achieved a 93.8% cure rate with repeated duodenal infusions.<sup>7</sup> A single-centre, retrospective study, assessing 18 patients, identified a 94% cure rate when using donor samples from patient relatives.<sup>9</sup> However, due to its small sample size and retrospective nature, this study should be interpreted with caution. In contrast, the use of faeces from unrelated donors did not differ the cure rate significantly.<sup>5</sup> Vancomycin is regularly used in CDI due to its superior efficacy for moderate-to-severe cases compared to metronidazole.<sup>10</sup> yet single-drug therapy has a cure rate of as little as 31%.<sup>7,11</sup> However, patients who were treated with both vancomycin and FMT had a cure rate of 94%, highlighting the significance of FMT use.<sup>7</sup>

Current routes of administration are via the nasogastric tube (NGT) or a colonoscopy.<sup>12</sup> Although NGT has been voted most unappealing by patients,<sup>13</sup> it has a reported success rate of between 80-94%.<sup>5,7</sup> whilst administration via colonoscopy has a reported 100% success rate.<sup>5</sup> These cure rates are reported in studies with small samples sizes, therefore larger comparative studies should be performed to provide more accurate and reliable results.

### Is bacterial diversity the key?

Understanding the precise mechanisms of bacterial diversity is key to understanding the pathogenesis of CDI,<sup>14</sup> and may aid the development of future treatments beyond FMT, such as stool substitute<sup>15</sup> or a pill.<sup>13</sup> A microbial diversity study using gene sequencing noted that patients with CDI had fewer taxa and a greater abundance of Proteobacteria species.<sup>14</sup> A subsequent study involving 20 subjects supported this finding, with a consistently low mean diversity prior to FMT.<sup>5</sup>

A decrease in butyrate-producing bacteria which utilise lactate could be the reason for this alteration in diversity and subsequent onset of CDI.<sup>14</sup> Butyrate has been associated with tissue development and repair, whereas accumulation of lactate has been linked with other dysbiotic gastrointestinal conditions such as ulcerative colitis.<sup>16,17</sup> This suggests that lactate-utilising bacteria (eg. Lachnospiraceae) might be key for combating CDI. Further RCTs are required to investigate the effects on diversity richness using lone bacterial species instead of the whole microbiota.

### Challenges of FMT and adverse effects

FMT is yet to have a definitive, widely accepted protocol, which poses a challenge for its acceptance among the medical community. The danger is that in the absence of available treatment via the NHS, many patients affected with recurrent CDI may search for similar FMT-based therapies via unproven internet sources.<sup>5</sup> Patient consent is also an issue, with 19% of patients refusing transplantation due to the unappealing aesthetics of faeces.<sup>13</sup> Stool samples obtained about six hours' prior to implantation tend to be used,<sup>7</sup> however, this timing is impractical and a recent study with 90% success rate showed that the use of frozen inoculum is as beneficial as the fresh sample.<sup>5</sup> The use of frozen inoculum could abolish the need to screen and select donors for every transplant and promote the use of a 'universal donor'. Adverse effects, which until recently haven't been recorded, should also be considered. Diarrhoea, cramping and belching have been reported post procedure, however, it is unclear whether FMT is the cause.<sup>7,8</sup> More recently, an isolated instance of bacteraemia was described after FMT through a colonoscopy.<sup>18</sup> Again, it is unclear if this complication occurred due to the FMT or the colonoscopy procedure.

### Conclusion

FMT has the potential to become a beneficial therapy, with a cure rate of 80% to 100% for patients with CDI and other dysbiotic conditions such as ulcerative colitis. Investigation of the finer points of stool handling and storage has provided the exciting possibility of using frozen inoculum. The understanding that bacterial diversity might play a big role in the pathogenesis of CDI will provide helpful guidance on how to proceed with FMT development. The question of whether a single species colony could be used instead of the whole microbiota remains unanswered. At the forefront of research, however, should be the analysis of possible adverse effects.

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# Early diagnosis is crucial: the Swindon experience of diagnosing and managing aortic dissection

By Gareth Morgan and Sophie Herbert

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Aortic dissection is a life-threatening condition involving a tear in the major artery from the heart, the aorta, with mortality as high as 20% pre-admission to hospital, and 27 to 30% in-hospital mortality. This study reviews the presentation, diagnosis, management and outcome of aortic dissection over the past five years at the Great Western Hospital, Swindon. We found that two-thirds of patients were initially misdiagnosed, due to common presenting symptoms, and a mortality of almost 40%. These results emphasise the importance of considering aortic dissection at initial presentation, to help minimise delay in intervention.

## Introduction

The aorta is the essential artery in transporting blood to the body and its organs.

The arterial structure consists of the innermost intima, the smooth muscular tunica media and the outermost adventitia. Aortic dissection is a tear in the intimal layer of the vessel wall. The Stanford classification divides aortic dissection into two types, A and B, according to involvement of the ascending aorta (Figure 1).

Formation of a false lumen can lead to obstructed blood flow and reduced organ perfusion, making this a life threatening condition. Pre-hospital mortality is reported as 20%, whilst in-hospital mortality ranges between 27-30%.<sup>2</sup> Importantly, early intervention can significantly reduce mortality in the first few days after presentation.<sup>2,3</sup>

Currently, the management of aortic dissection is restricted by the variability in presentation and difficult clinical recognition. Typically, it presents as a 'tearing' or 'ripping' pain, radiating to the back.<sup>4</sup> However, these 'classical' features are absent in many cases.<sup>3</sup>

If aortic dissection is considered, CT imaging has high specificity and sensitivity for its diagnosis.<sup>2</sup> Treatment is dictated by dissection type (A or B). Surgery is indicated for most type A cases, with mean five year survival rates reported as 73%.<sup>2</sup> Meanwhile, there is consensus that type B dissections are best managed medically unless a complication develops (rupture, visceral/limb ischaemia, refractory pain or uncontrollable hypertension).<sup>2</sup>

This study aimed to evaluate common presenting features and the current management of aortic dissection at the Great Western Hospital, Swindon.

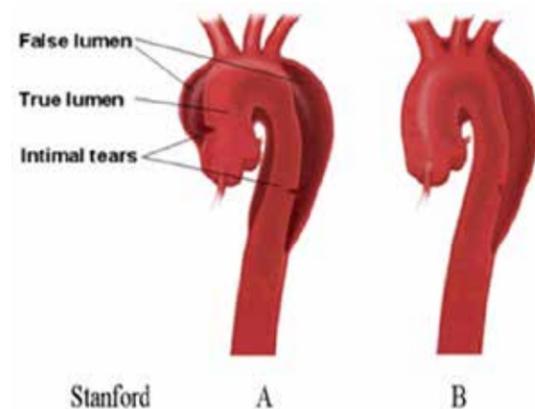


Figure 1: Stanford classification of aortic dissection. Type A involves the ascending aorta. Type B is when there is no involvement of the ascending aorta<sup>1</sup>

## Methods

Data were collected from medical notes of all patients with aortic dissection presenting at the Great Western Hospital, Swindon between July 2010 and July 2015. Emergency/acute and chronic cases were included. Patients with a known diagnosis of aortic dissection prior to July 2010 were excluded. Variables investigated were: time of presentation; symptoms; initial diagnosis; type interventions; and outcome. Datasets for certain variables were incomplete, and denominators are given where appropriate. Students' t- and Chi squared statistical tests were used for analysis. Generally patients were split into types A and B; emergency and chronic; and <65 years and ≥65 years (see Table 1).

	All Patients (n=33)	Type A (n=17)	Type B (n=13)	Emergency (n=22)	Chronic (n=8)
Mean Age (SE) (Years)	73.3 (2.3)	72.5(2.6)	72.6 (4.5)	69.1 (3.0)	80.6 (4.8)

Table 1: Comparison of patient demographics by group. SE = Standard error.

## Results

33 patients were included. Data on type A/B were unavailable for three patients, while 3 patients weren't classified as emergency or chronic.

Type A and B cases were similar in age (p = 0.77), but emergency cases occurred in a younger population compared to chronic cases (p = 0.002). There was no significant difference in gender between types A and B (p = 0.63), or between emergency and chronic (p = 0.46).

Male, n (%)	15 (45.5)	7(41.2)	7 (53.8)	10 (45.5)	3 (37.5)
Female, n (%)	18 (54.5)	10(58.8)	6 (46.2)	12 (54.5)	5(62.5)

## Presenting Features

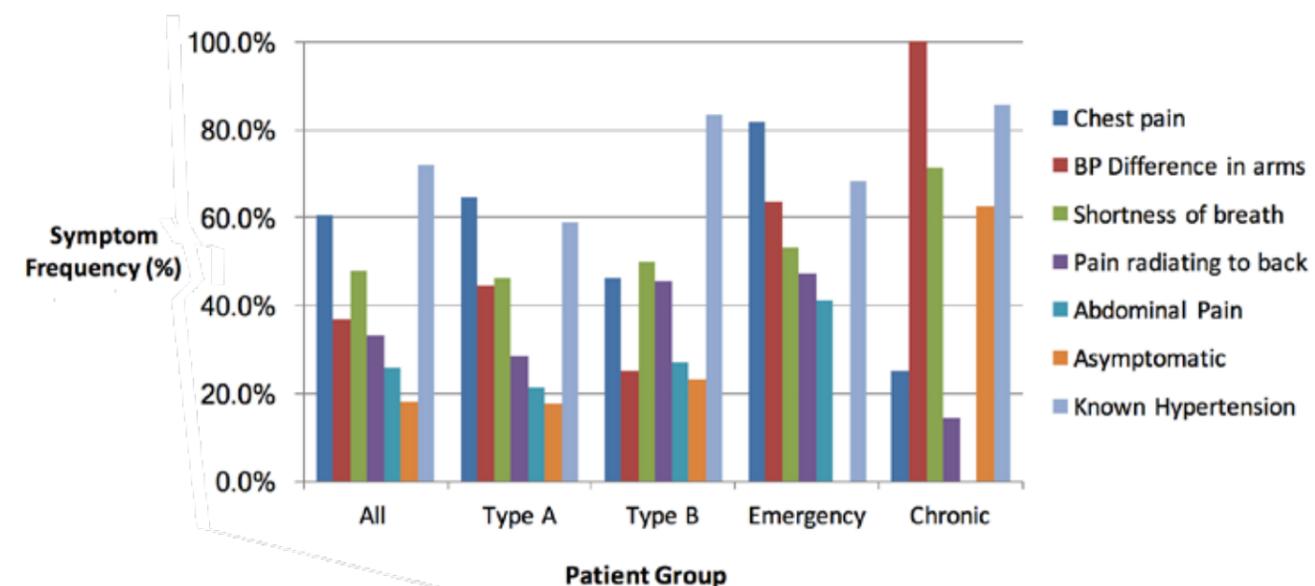


Figure 2: Frequency of presenting features in the different patient groups. BP = Blood pressure.

The most prevalent presenting features were: known hypertension, 23/32 (71.9%, SE=7.9%); chest pain 20/33 (60.6%, SE=8.5%); and breathlessness 12/25 (48.0%, SE=10.0%). There were no significant differences between the presentations of types A and B. Chest pain was more frequent in emergency than chronic cases (81.8% (95% CI, 60.9-93.3) vs 25.0% (95% CI, 6.3-59.9), p = 0.01).

### Diagnosis

Initial misdiagnosis occurred in 22/32 (68.7%) of cases. In emergency cases only, this was associated with a prolonged time to diagnosis confirmation, compared to cases in whom aortic dissection was considered at initial presentation ( $p = 0.02$ ) (Table 2). Frequency of misdiagnosis was not associated with age, gender or type.

Times (hh:mm:ss)	Initial Diagnosis	Misdiagnosis	P-value
Admission to diagnosis* (SE) (ID, n=7; MD, n=11)	02:04:00 (00:26:00)	26:41:33 (09:07:18)	0.02

**Table 2:** Time from admission to diagnosis for cases in which aortic dissection was considered at initial presentation (Initial diagnosis) and those in which an alternative diagnosis was initially considered (Misdiagnosis). \*Incomplete dataset. n= number of patients for which data were available in each group. ID= initial diagnosis, MD= misdiagnosis, SE=Standard error.

### Management and Outcome

Type A cases were managed conservatively in 6/15 (40.0%), or surgically, 7/15 (46.7%), while 2/15 (13.3%) died before initiation of management. Data were unavailable for the other two type A cases. All type B patients were managed conservatively.

Although mortality was greater in type A compared to type B cases (Table 3), this difference was not significant (47.1% (95% CI, 26.2-69.0) vs 15.4% (95% CI, 3.1-43.5),  $p = 0.07$ ).

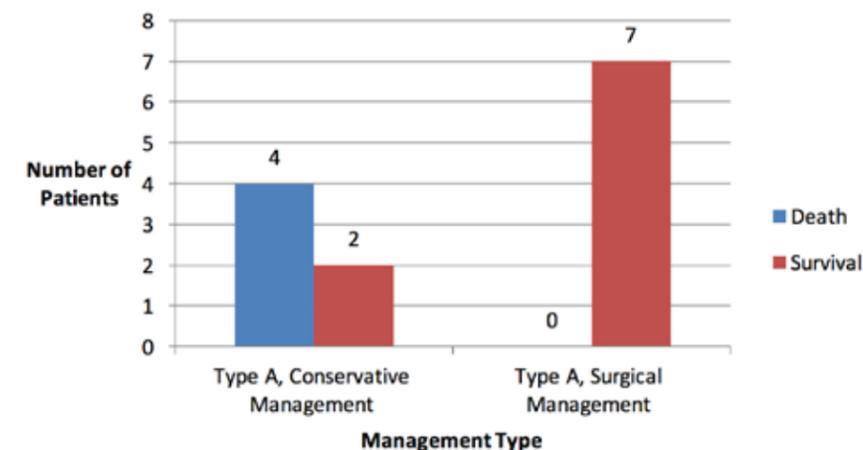
Age ( $p = 0.69$ ), gender ( $p = 0.54$ ) and day of presentation (Table 4) were not predictors of mortality. Surgical management of emergency type A dissections significantly reduced mortality compared to conservative management (0/7, 0.0% vs 4/6, 66.7% (95% CI, 29.6-90.8),  $p = 0.02$ ).

	All Patients (n=33)	Type A (n=17)	Type B (n=13)	Emergency (n=22)	Chronic (n=8)
Death, n (%)	13 (39.4)	8 (47.1)	2 (15.4)	10 (45.5)	3 (37.5)
Survival, n (%)	20 (60.6)	9 (52.9)	11 (84.6)	12 (54.5)	5 (62.5)

**Table 3:** Comparison of mortality by patient group.

	Weekday (n=14)	Weekend (n=8)	$p = 0.75$
Death, n (%)	6 (42.9)	4 (50.0)	
Survival, n (%)	8 (57.1)	4 (50.0)	

**Table 4:** Comparison of mortality for patients presenting on weekdays and on the weekend.



**Figure 3:** Frequency of death and survival in emergency type A dissections managed conservatively or surgically.

### Discussion and Conclusion

In concordance with data from the International Registry of Aortic Dissection (IRAD), this study demonstrated known hypertension, chest pain and shortness of breath to be common presenting features of aortic dissection.<sup>3</sup> Since these features are associated with other, more common, conditions, such as myocardial infarction, it may not be surprising that 68.7% of patients in this study were misdiagnosed at presentation. Although this may be overestimation, owing to the inclusion of incidental cases, misdiagnosis rates have been reported as high as 38%.<sup>5</sup> Our results further emphasise the importance of considering aortic dissection at initial presentation. This reduces time to diagnosis confirmation thus minimising delayed intervention.

The mortality in this study was almost 40%, slightly higher than in data from IRAD, which reported in-hospital mortality as 27.4%. Despite this, our results highlight the potential to improve outcomes of emergency type A aortic dissection with surgical management.

Given its low incidence and variable presentation, aortic dissection may continue to be the needle in the haystack. Referral pathway development and introduction could increase awareness and efficiency of management by ensuring appropriate and rapid intervention.

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# Aetiology of Bell's Palsy: The Viral Hypothesis

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**My first clinical experience was a maxillofacial placement. During this time, I often encountered the condition of Bell's palsy. Talking to patients made me realise the impact BP can have on a patient, and how severely it can affect their quality of life. Most patients would be very distressed and would want to know why it has happened, how it should be treated and how long it will take for them to recover. These experiences, as well as independent learning, inspired me to write this article.**

*Saniya Abid*

## Abstract

**Bell's palsy is a condition in which there is paralysis of the facial nerve, usually on one side of the face. It affects 1 in 5000 people annually, and 30% of cases do not resolve spontaneously. This patient group risks major complications such as permanent paralysis and pain. The cause of BP remains unknown although most studies point to a viral cause. This article will concentrate on the hypothesis that Bell's palsy is caused by the Herpes simplex type 1 virus, and looks at possible mechanisms. The importance of finding the aetiological agent is crucial in treating unresolved cases.**

## Introduction

Bell's palsy (BP) is an acute paralysis of the facial nerve of unknown origin, and is diagnosed clinically – there is no specific test for the condition. It commonly affects people aged between 15-60 years,<sup>1</sup> though it can happen at any age.<sup>2</sup> Symptoms include unilateral paresis or paralysis, irritation of the eye and earache on the affected side, and an altered sense of taste.<sup>1</sup>

## Method

A variety of databases such as PubMed, Science Direct and Cochrane were searched using the terms 'Aetiology of Bell's Palsy', and 'Herpes simplex virus and Bell's Palsy'. Textbooks were also consulted.

## Results and discussion

BP is caused by inflammation of the facial nerve as it passes through the facial canal, causing compression and ischaemia. This leads to a blockage of nerve signal transmission and demyelination.<sup>3,4</sup>

BP was first thought to be linked to viral agents due to its shared features such as its potential for epidemic-like spread, flu-like symptoms and gadolinium enhancement of the facial nerve, during its acute phase, particularly during the acute phase of Bell's palsy, suggesting inflammation due to infection.<sup>5</sup> The list of possible viral aetiological agents includes adenoviruses, mumps and the herpesvirus family (Herpes simplex virus 1, Herpes simplex virus 2 and Varicella zoster virus).<sup>6</sup>

The herpesviruses are DNA viruses that characteristically have the ability to establish lifelong latency in humans and can periodically reactivate despite a working immune system.<sup>7-10</sup> Members of this family have a common structure but vary in size.<sup>7,11</sup> Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2) and Varicella zoster virus (VZV) are described as neurotropic (i.e. they establish latent infection in the peripheral nervous system and the viral genome maintained in peripheral sensory ganglia).<sup>6,8,9</sup>

## HSV-1

The pathogenesis of HSV-1 includes entry via skin or mucous membrane. The virus will then replicate in the epidermis or dermis and gain entry into sensory or autonomic nerve. Following entry it will be transported into the neurons in the ganglia. This is known as the primary infection and at this point lifelong latency is established.<sup>12</sup> The viral genome will now be maintained here and act as a reservoir for viral nucleic acids.<sup>6</sup> HSV-1 causes recurrent episodes of blisters on the mouth and lip due to its reactivation in the trigeminal ganglia, and the inferior and superior cervical ganglia.<sup>12</sup>

Herpes simplex virus (HSV) was first postulated as the aetiological agent by McCormick in 1972.<sup>9</sup> The theory

stated that the virus colonizes the peripheral axon which offers the virus protection from antibodies and mononuclear infection. HSV would then rupture from the nerve axon, infect the Schwann sheath and progress centripetally. BP would be preceded by swelling, caused by herpetic endoneuritis, which would reach the enclosed space of bony fallopian canal, thus resulting in facial nerve compression and subsequent paralysis.<sup>9</sup> Reactivation of the virus would then lead to nerve damage.<sup>6</sup>

20 years later, two studies identified the presence of HSV-1 nucleic acids in the geniculate ganglion of the facial nerve.<sup>10,13</sup> One found 56% of latent HSV-1 in 10 and another found 88% in tissue from autopsy cases.<sup>12</sup> However, latent HSV-1 was also found in other cranial ganglia.<sup>10,13</sup> The HSV-1 theory was further supported by the detection of HSV-1 in the endoneurial fluids of idiopathic facial paralysis patients during surgical decompression surgery.<sup>6</sup> No HSV was found in the control groups.

However, it is important to acknowledge that a virus' presence does not imply that it is a causative agent.<sup>14</sup> Furthermore, a small sample size of 14 patients may significantly reduce reliability. Triggers that may have induced HSV-1 reactivation may also have caused BP, such as the surgical procedure itself, although this is unlikely because the endoneurial fluid and muscle samples were taken within two hours of the surgery starting.

HSV has received a lot of attention due to the high frequency of elevated antibody titres in patients.<sup>15</sup> But this can be explained as an increased nonspecific response resulting from polyclonal activation of memory B cells from another trigger.<sup>14</sup> Animal experiments have further drawn attention to HSV's ability to induce facial paralysis. One study, for example, showed that inoculation with HSV-1 into mice auricles led to 60% of mice showing facial paralysis with demyelination in descending motor roots.<sup>17</sup> As always, however, caution should be exercised when using data from studies involving animals.

## VZV

VZV has also been investigated as it is the causative virus in Ramsey Hunt syndrome, an important differential diagnosis for BP.<sup>3</sup> Serological data have revealed evidence of VZV and HSV reactivation. One

study showed VZV reactivation was found in 8% of BP patients (23/ 296 participants),<sup>12</sup> while another identified HSV reactivation in 18% of patients. In a separate study, 150 patients were virologically examined and reactivation of HSV-1 or VZV was observed in 34% them.<sup>18</sup> It is crucial to note the limited sample size. One article speculates HSV involvement to occur in 31-79% of patients with BP.<sup>19</sup>

It is now thought that latent herpesvirus reactivation, or an infection from another virus, causes an autoimmune reaction against peripheral nerve myelin components leading to demyelination of the facial nerve. However, the process by which this occurs is still not clear.<sup>6</sup> Criticisms of the HSV-1 hypothesis include: that HSV-1 mucocutaneous reactivation is not associated with motor impairment; cold sores are common and recurrence rates are relatively high, whereas BP is usually an isolated episode and rare.<sup>6</sup>

## Antiviral therapy

There are conflicting results as to whether antivirals are effective as a combination therapy. Guidelines from the National Institute of Health and Care Excellence (NICE), based on a variety of meta-analyses and a randomised controlled trial, recommend prescribing the anti-inflammatory prednisolone if the individual is presenting within 72 hours of onset.<sup>20-23</sup> However, the current approach to antiviral therapy has no significant benefit despite the probable involvement of herpesviruses<sup>20,23,24</sup> and NICE does not generally recommend antiviral therapy, alone or in combination with prednisolone.<sup>24</sup> However, a new study has shown that the addition of an anti-viral to oral corticosteroid treatment may be associated with recovery in a higher proportion of patients, at 3-12-month follow-up, compared to treatment with corticosteroids alone.<sup>25</sup>

## Conclusion

It seems probable that BP is caused by a herpesvirus, most likely HSV-1 or VZV. And there is also reasonable evidence supporting the existence of an autoimmune process, which may or may not be linked to viral infection. Posing these questions are more than theoretical. They are important for supporting research into the use of antivirals as therapeutic agents. Although current clinical guidelines do not recommend the use of antivirals for the treatment of BP, more research is needed in future to determine the potential benefits of antiviral treatment.

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# Comparing subjective and objective memory measures for patients with neurodegenerative disease

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## Introduction

**Dementia affects almost a million people in the UK with an associated economic impact of over £26 billion per annum.<sup>1</sup> It is a disease that can be difficult both to diagnose and monitor due to the paucity of available biomarkers and the unreliable association between cerebral atrophy shown by imaging, and day-to-day function. Thorough neuropsychological assessments can measure more subtle cognitive changes but they require expert administration and are time consuming. Questionnaires, on the other hand, provide a fast and easily attainable source of information when evaluating dementia sufferers. However, previous conflicting research has rendered the clinical utility of such reports uncertain.<sup>2,3</sup>**

**It is often a familiar paradox for clinicians at the memory clinic that the most concerning patients are those that don't tend to worry about their memory. This stems from the common observation that dementia is accompanied by Anosognosia, the loss of awareness into the toll of the disease. Not only do their cognitive faculties fail but also their own introspective evaluation of them. This 'metamemory', the ability to evaluate accurately the quality of one's own memory, is instrumental to healthy cognitive function. Impaired metamemory accelerates loss of independence in activities of daily living as the patient fails to recruit memory-aiding behaviours to compensate for their memory**

## Methods

Neuropsychological data were obtained retrospectively from the notes of 61 dementia patients who attended the memory clinic at the Southmead Hospital Brain Centre in Bristol, and collated into an anonymised Excel spreadsheet. Patients had given prior consent to having their data used for research purposes and an independent ethics committee had approved the study. Huntington's disease and frontotemporal dementia patients were excluded from the datasets due to the potential impact of behavioural change on self-report scales. Inconsistent reporting of variables and differences in self-reports of memory, derived

failings.<sup>4,5</sup> Consequently, a dementia patient's opinion of their own memory may not reflect the actual level of function but instead other factors such as their mood.<sup>2,3,6</sup>

**The Prospective and Retrospective Memory Questionnaire (PRMQ) assesses a patient's beliefs about their own memory function in everyday life. It contains 16 questions asking how likely a memory failure is to occur, using a 5-point scale. It covers both short-term and long-term memory, as well as self-cued and environmentally cued memory. We designated patients' self-assessment scores as PRMQ1.**

**This INSPIRE research project investigates the hypothesis that the PRMQ1 and objective memory test scores do not correlate. Separately, we will also test the hypothesis that worse mood correlates with lower PRMQ1 scores.**

**A patient's carers can provide a valuable alternative source of information, and their judgement may prove more accurate than that of the patient. However, previous research has often neglected this valuable resource. We set out to test the hypothesis that the carer's opinion does correlate with objective memory scores by comparing scores provided by carers with objective memory scores.**

from PRMQ1 data, were converted to a T-score using normative data.<sup>7</sup>

Patients were classed as having depressive symptoms if they scored  $\geq 14$  on the 'Depression Anxiety and Stress Scale-42' (DASS-42) or  $\geq 10$  on the 'Patient Health Questionnaire-9' (PHQ-9).<sup>3</sup>

Carers' views were sourced either from the PRMQ2 or the 'Memory and Concentration' subsection of the 'Cambridge Behavioural Inventory-Revised' (CBI-R).

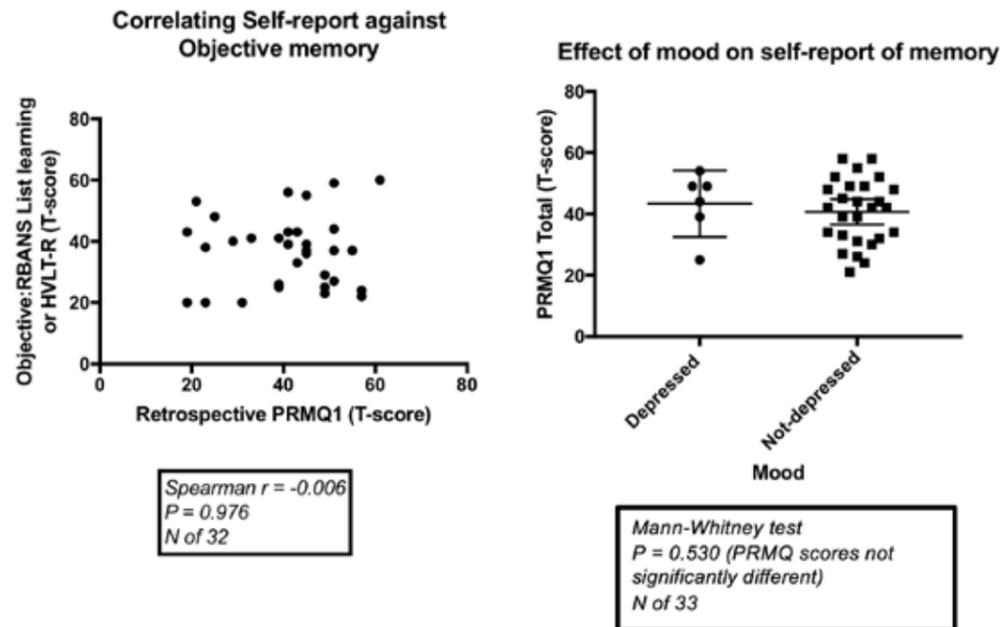
The 'Hopkins Verbal Learning Test-Revised' and the List Learning subsection of the 'Repeatable Battery for the Assessment of Neuropsychological Status' (RBANS) were used as measures of objective memory performance. The results from the immediate recall, rather than the delayed recall, were used in order to generate a better spread of data without a floor effect.

The T-scores of the two data sets were combined with the assumption that the normative datasets for each test were similar. The data were statistically analysed using Prism 7.0 software.

## Results

### Self Report

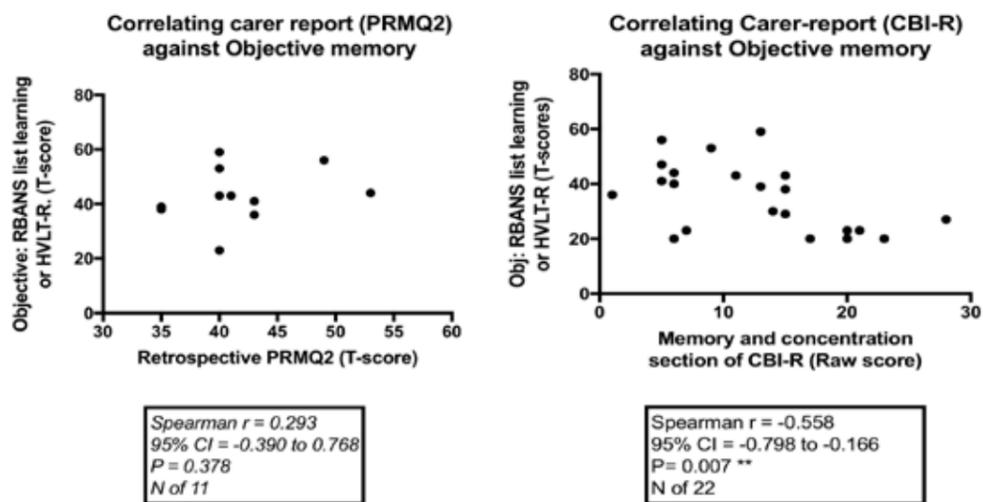
In patients with neurodegenerative disease, self-reported quality of memory, as gauged by the PRMQ1, had no relation whatsoever to the objective measures of memory functioning. The presence of depression had no apparent effect on PRMQ1 score.



### Carer Report

Greater carer concern on the memory section of the CBI-R (generating a higher raw score) significantly correlated ( $P=0.007$ ) with a lower performance on objective tests (Spearman  $r = -0.558$ ).

A similar but statistically insignificant ( $P=0.378$ ) effect was seen when comparing the PRMQ2 and objective scores. A lesser PRMQ2 score, indicating a subjectively worse cognitive function, corresponded to a lower objective memory score (Spearman  $r = -0.293$ ).



## Discussion

Our finding that self-report does not correlate with objective assessment of memory is consistent with previous findings.<sup>8-10</sup> However, the lack of relation between mood and PRMQ1 score conflicts with previous findings.<sup>11-13</sup> However, considering the scarcity of depressed patients in the available dataset, this could be the result of an underpowered statistical comparison.

Our work confirms that carer report, in particular derived using the CBI-R, strongly correlates with objective neuropsychological assessments. This validates the inclusion of carer report in the evaluation of memory function. We found that PRMQ2 followed the same pattern but lacked statistical significance, most likely because the dataset was only half the size.

In an aging population with a climbing prevalence of dementia, the community will increasingly be responsible for evaluating and managing this condition. In the community setting, where neuropsychological assessment is not possible, carer report should be used as an additional tool to enhance clinical acumen.

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**The generous INSPIRE grant has provided me with opportunity far beyond this piece of data-analysis. It facilitated a summer at Southmead Hospital's warm and welcoming Brain Centre. From blinding studies by mixing medication to attending lunchtime talks, this taster into the internal workings of a research team has fed my desire to pursue an academic career. Thanks to the help of those at the Brain Centre, I started my Academic Foundation Programme studying neuropsychopharmacology in August 2017.**

*Jack Thompson*

# The impact of child sexual abuse on mental health, wellbeing, social welfare, and integration into society

By Andi Stanescu

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Child sexual abuse is a traumatic experience with complex repercussions. This paper will examine the detrimental impact of CSA on mental health and interpersonal functioning, as well as explore the negative psychobiological consequences. The psychological effects of CSA include depression, anxiety, sexual behaviour problems, post-traumatic stress disorder (PTSD), and dissociative disorders. Therefore, it is vital to explore and address the issues around CSA and use this understanding in giving better help those affected. This article focuses on the psychophysiological consequences of CSA and its implications for the individuals' later integration into society.

## Introduction

Child sexual abuse (CSA) is defined as "forcing or enticing a child to take part in sexual activities whether or not the child is aware of what is happening".<sup>1</sup> An NSPCC survey found that 11.3% of young adults (aged 18-24) in the UK, had experienced sexual abuse during childhood.<sup>2</sup> Females are more likely than males to be victims of CSA; on a global scale approximately 7.9% of males and 19.7% of females experience CSA before the age of 18.<sup>3</sup> CSA survivors have an increased risk of mental health problems as well as difficulties integrating into society as adults compared to non-abused peers.<sup>4</sup> This article will review the evidence surrounding the impact of CSA on psychological and neurological functioning, with a focus on the psychopathologies that affect victims throughout their lives.

## Method

Evidence for this article was identified through a literature search of Medline, Sciondirect, Google Scholar, BjpPsych, and Cochrane Library databases. The searches were performed without application of any language restrictions, with publication dates from January 1, 1984 to January 1, 2017. Overall, 47 studies were identified using the key words present in the title or abstract: "child sexual abuse", "child sexual maltreatment", "mental health", "CSA", "wellbeing", "social welfare" and by manual searching of references. Studies were excluded if they lacked conclusive results or clear definition of CSA, and if they were not conducted exclusively on patients with CSA.



## Discussion

### Psychological impact of CSA

CSA can have wide-ranging consequences. Recent evidence highlights the vast differences in symptoms that many victims manifest, and which are not confined to mental health.<sup>5</sup> The effects of CSA are complex and include up to a five-fold greater likelihood of being diagnosed with at least one anxiety disorder compared to their non-abused peers,<sup>6</sup> being more than four times as likely to be diagnosed with major depression, post-traumatic stress disorder (PTSD), personality disorders,<sup>7</sup> and eating disorders.<sup>8</sup> While some of these are indirect consequences, 42-90% of individuals who experienced CSA develop PTSD. In one study 50% of CSA victims met either full or partial PTSD criteria showing that symptoms of PTSD are common in the first months after the trauma is experienced.<sup>9</sup> The relationship between the abuser and the victim could play an important role, as survivors of CSA where the abuser is a close relative consistently present with longer-term psychological problems.<sup>10</sup> Symptoms of dissociation have been documented among victims of CSA across multiple age groups. When compared with non-abused children, CSA victims have been eight times as likely to present with significant and enduring levels of dissociation.<sup>11</sup> However, this might not affect all CSA victims, as dissociation tends to characterise particularly severe cases where the victim suffered repeated abuse that involved multiple perpetrators.<sup>12</sup>

### Sexual abuse scars the brain in specific ways

Trauma can change the brain's neuroplasticity and structure. Alexander describes CSA as a "chronic neurologic disease" and argues that the effects produce decades of negative outcomes for survivors.<sup>13</sup> Brain areas associated with consciousness and complex cognitive functions, particularly the prefrontal cortex, are consistently smaller in adults who had been abused as children, according to MRI-based cortical thickness analysis.<sup>14</sup> Areas found to be affected include the corpus callosum, which affects the integration of the cerebral hemispheres, and is associated with mood instability and personality shifts.<sup>15</sup> Furthermore, CSA victims show deficiencies in executive functioning, attention, increased impulsivity, and abstract reasoning, as well as cognitive impairment, poor academic performance, and verbal deficits.<sup>16,17</sup> This would suggest that CSA has negative effects on brain functioning that are identifiable decades later. This could be explained by a reduction in hippocampus volume due to increased levels of stress hormones, primarily cortisol, produced by the child

as a response to abuse.<sup>18</sup> The hippocampus converts short-term memories into long-term ones, which might explain the enduring changes found in the child's ability to retain and use information.

### CSA, social welfare, and integration into society

Bird and Kelly proclaimed that "overall, the adults we become are a result of our childhoods".<sup>19</sup> CSA is correlated with tendencies such as fear of intimacy, passivity, difficulties in establishing boundaries, which in turn hinder the establishment and maintenance of positive interpersonal relationships.<sup>20</sup> Adults victimised as children may see themselves as not worthy of good and healthy relationships, which might impair their initiation of social interactions.<sup>21</sup> It is possible that following the breaches of trust and the exploitation that characterise CSA, victims develop insecure or disorganised attachment styles.<sup>22</sup> They may tend to struggle with instability, particularly in their closest relationships.<sup>23</sup>

**"I turned my anger and hate inwards. I came to despise myself"**<sup>24</sup>

The offender's grooming can have the effect of decreasing self-esteem and increasing self-blame,<sup>25</sup> which is particularly significant for victims of more severe forms of CSA who, on average, are more likely to have negative expectations of the future and believe they cannot influence external events. This decrease in self-esteem, a worry of consequences from the abuser, fear of the possibility of experiencing abuse again, self-blame, victim blaming by other members of society, and a lack of positive expectations of the future could be linked with the reluctance of children to disclose the abuse.<sup>10,26</sup> These long-term effects continue into adolescence and adulthood, resulting in increased difficulty to integrate into society.<sup>27</sup>

## Conclusion

Sexual abuse in infancy and early childhood damages the fundamental processes that normally form the building blocks of solid personality growth and interpersonal relationships. CSA appears to have prolonged effects on cognitive performance and can prompt maladaptive behaviours with unwanted repercussions in the long-term. CSA does not create a separate distinguishable condition, but instead produces a diversity of pathological and symptomatic behaviours. Conditions such as depression, anxiety, and PTSD all play a role in this complex mechanism of progressive damage. Furthermore, preliminary evidence proposes that CSA results in volume reductions in the frontal cortex, hippocampus, corpus callosum, and also dysregulation of stress hormone production. Looking to the future, research in neurocognitive development will fill crucial gaps in our understanding of the wide-ranging damage produced by CSA enabling us to address these issues better and aid the rehabilitation of those affected.

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# Research method: Morphological apoptotic assay

By David Li, Timothy Woo and Chris Pepper

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**This paper describes the use of the morphological apoptotic assay to assess the action of an experimental small molecule inhibitor drugs for their ability to kill chronic lymphocytic leukaemia cells in vitro. The drugs belong to a class of inhibitors of the enzyme IKK-alpha, which is constitutively active in CLL cells. We aim to facilitate a better understanding of the process of apoptosis, and introduce one of the many experimental methods available to quantify this process ex vivo – an important step in assessing the potential usefulness of novel anti-cancer agents prior to their progression to clinical trials.**

## Introduction

Chronic lymphocytic leukaemia (CLL) is one of the most common haematological malignancies in the western world and as yet no curative agent has been identified.

We were interested in exploring an area of research around the use of novel drugs known as small molecule inhibitors. These are very much under scrutiny owing to their potential as 'targeted therapies' against cancer that attempt to limit toxicities seen in conventional chemotherapies.

We focused on a technique known as the Annexin V / 7-AAD morphological apoptosis assay, which is important and relevant to various pre-clinical fields besides exploring the efficacy of anti-tumour drugs. The Annexin V / 7-AAD apoptosis assay is a relatively straightforward laboratory technique designed to allow researchers to quantify the degree of cell death in a defined population of cells.<sup>1</sup>

Apoptosis is the homeostatic process of controlled programmed cell death, which aids the removal of damaged or unwanted cells. It is characterised by loss of membrane integrity, followed by

cytoplasmic shrinkage and – in vivo – the phagocytosis of apoptotic bodies by macrophages.<sup>2,5</sup> The early structural changes in the membranes of apoptotic cells cause the exposure of phosphatidyl serine (PS), which in turn can be labelled by its naturally occurring ligand, Annexin V.<sup>1,2,5,6</sup> During late apoptosis membrane permeability is disrupted, permitting the binding of 7-ADD to DNA.<sup>7</sup>

There are multiple methods to assess apoptosis. We conducted the following experiments to test pre-clinically the efficacy of novel drugs against CLL cells. The procedure described below focuses on the use of an Annexin V-FITC / 7-AAD kit for the assessment of apoptosis induction by experimental anti-leukaemia drugs.

The drugs used in this assay (including SU1349) are novel agents which act as inhibitors of IKK-alpha, a kinase involved in the NFκB pathway, which is constitutively activated in CLL cells and is vital for tumour cell proliferation and survival. The therapeutic goal is to disrupt the NFκB pathway in order to produce an anti-tumour response.

## Methodology

**1)** Preparation. The CLL cells were derived from samples of patients' peripheral blood. Mononuclear cells were isolated and aliquots placed in culture plates or tubes at a final concentration of 1 million cells / mL.

Subsequently, different concentrations of the novel drugs were added to each cell culture in order to derive a dose-response. These cells were then allowed to incubate for 48 hours so that the drugs could exert their desired apoptotic effects.

**2)** Cell extraction. After the incubation period, the contents of each well were harvested into separate Eppendorf tubes and centrifuged for five minutes at 300 x g, in order to pellet the cells. The liquid supernatant was poured off.

**3)** Annexin V / 7-ADD labelling. The cells were first re-suspended in a calcium-rich buffer to enable the Annexin V ligand to bind to PS. Next, Annexin V and 7-AAD were added to each aliquot of cells prior to incubation in the dark for 10 minutes.

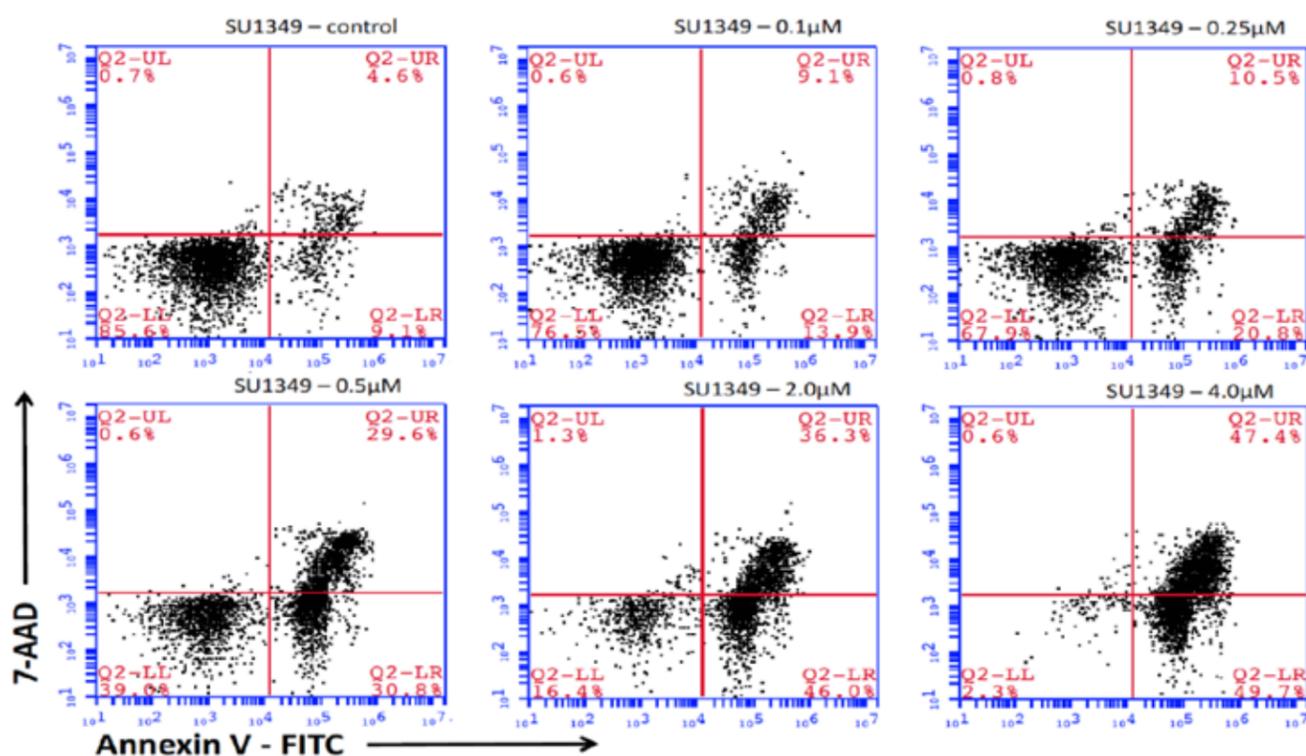
**4)** Finally, to visualise these stains and quantify the degree of cell death, the cells were put through a flow cytometer to detect the fluorescence emitted from the stained cells.<sup>8</sup>

## Results

For a given drug concentration, the longitudinal 7-AAD axis was plotted against the horizontal Annexin V axis, with each dot representing cells. The graph was split into four quadrants and the results calculated as a percentage. Low values for both 7-AAD and Annexin indicated cells that had not apoptosed. High Annexin with low 7-AAD would indicate early apoptotic cells; high Annexin and high 7-AAD would indicate the proportion of late apoptotic cells. The overall percentage of apoptosed cells was determined by summing the quantity of early and late

apoptotic cells (Fig.1).

Ideally, we would want the experiment to display dose-dependent results where the degree of apoptosis increased with the drug concentration. Thereafter, we could then obtain the LD-50 values (concentration of a certain drug required to bring about 50% of apoptosis in the population of leukaemic cells) for the drugs, visualised through the graphical representation of a sigmoid curve.<sup>3,4</sup>



**Figure 1:** Individual flow cytometry results for a certain drug (SU1349) at escalating concentrations of 0 (control), 0.1, 0.25, 0.5, 2.0 and 4.0 M. As the drug escalates in its concentration, increasingly more cells can be visualised populating the upper and lower right quadrants, indicating a greater rate of apoptosis, both early and late. In the lower doses, most cells are converged about the lower left quadrant, signalling that the majority of cells are still alive. In order to derive a sigmoid curve to obtain LD-50 for SU1349, individual percentages of apoptosis are collected at each dose (calculated by summing early and late apoptosis rates) and projected into a graphical representation.

## Conclusion

This paper describes an experimental technique used to quantify the degree of apoptosis of CLL following incubation with novel biological agents. An Annexin V-FITC / 7-AAD kit was used; Annexin is an indicator of early apoptosis by binding phosphatidyl serine (PS), while 7-AAD signals is a DNA intercalating agent that signals late apoptosis. By assessing total apoptosis (early + late) at escalating doses of any particular drug, we can graphically derive a LD-50 value. A lower LD-50 value means that only a smaller dose of drug is required to

bring about 50% apoptosis, which in turn may mean that the drug in question has a stronger anti-cancer property. In future, drugs exhibiting promising pre-clinical therapeutic potential could progress to human clinical trials. Thus, an appreciation for the relevance of laboratory experimental methodologies is of vital importance in the field of drug development.

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# Side effects and overuse of Dovobet in patients with psoriasis

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This descriptive case series describes a group of patients who have all suffered from at least one side effect as the result of the use of Dovobet (calcipotriol/betamethasone dipropionate 50mcg/g & 0.5mg/g ointment or gel) ointment or gel, a common potent topical treatment for psoriasis.

**One dermatology consultant recorded all patients who had developed adverse reactions from Dovobet, despite short- to medium-term clinical trials showing it to be a safe treatment. Only short-term side effects such as rash, skin burning sensation and skin exfoliation are listed in the summary of product characteristics (SPC), yet potentially severe long-term Dovobet side effects have not been itemised by pharmaceutical companies.**

**The aim of this study was to explore the patients' reported side effects from Dovobet. The duration and frequency of the use of Dovobet were also noted, due to concern over patient adherence to medication and overuse of the product. Therefore, the use of Dovobet by specialists, GPs and patients was also explored.**

## Introduction

Psoriasis affects 1.3-2.3% of the population – both genders equally – and most commonly presents before 35 years old.<sup>1</sup> Plaque psoriasis is the most common form, affecting eight out of ten patients.<sup>2</sup> The pathophysiology of psoriasis is relatively unknown; it is a relapsing and remitting disease, commonly triggered by many lifestyle factors including smoking, stress, injury to the skin, hormonal changes, obesity and excess alcohol consumption.<sup>3</sup> Psoriasis is treated with a variety of topical and systemic remedies, but is incurable.

Dovobet is a combination topical preparation licensed as a third-line treatment for psoriasis on the scalp and a fourth-line treatment for psoriasis on the trunk, upper limbs and lower limbs; the product comes in either ointment or gel form.<sup>4</sup> Dovobet is licensed for a maximum of eight weeks' use.<sup>5</sup> Specialist advice must be sought should treatment last for longer than four weeks, as it has a number of contraindications.<sup>1</sup>



Tupungato/Shutterstock.com

## Method

This is a descriptive study looking at a series of 18 psoriasis patients under the care of one consultant dermatologist in one centre. Patients were identified over a four-year period, after showing a side effect from recent or on-going exposure to Dovobet.

The project involved looking at clinic letters, written case notes, electronic files and GP referral letters, and records on whether the patient reverted to using Dovobet and if the side effect settled. All patients were referred to the consultant by their GP following an increase in the severity of their psoriasis.

## Results

The mean duration of continual Dovobet use was 3.2 years. The most common side effects were destabilisation and rebound – well-known and predictable side effects of using a potent topical steroid to treat psoriasis. The least common side effects were erythema, rosacea and telangiectasia.

All 18 patients with side effects went on to have second- or third-line treatments (UVB or systemic therapy) after their exposure to Dovobet; six patients needed to have both UVB and systemic treatment.

In ten patients, despite further treatment including UVB and systemic therapy, the destabilisation of psoriasis has persisted to the present day.

The four patients who were prescribed methotrexate complained of worsening or continuing problems with their side effects despite the systemic therapy.

100% of the patient group had to withdraw from treatment of Dovobet due to the severity of their side effects.

## Discussion

Leo Pharmaceuticals publish the potential short-term side effects of Dovobet.<sup>6</sup> A patch test study investigated the safety of Dovobet use on mild to moderate psoriatic plaques by applying Dovobet gel repeatedly to a patch of skin for 21 days. It was stated, that no severe side effects were found from the continual application of Dovobet.<sup>7</sup> However, the long-term effects of such a potent steroid cream have not been documented. Published clinical trials were only conducted between eight and 52 weeks, despite evidence that a patient's use of Dovobet can be for longer.

The apparent safety of Dovobet demonstrated in clinical trials conflicts with the experiences in real life, as illustrated in this case series. The license and formulation, including a potent topical steroid of Dovobet, disregards the lifelong nature of psoriasis. It also ignores the ongoing need of patients beyond four-to-eight weeks, for a treatment they find acceptable and efficacious. Furthermore, neither Vitamin D analogues nor topical steroids can induce temporary remission in psoriasis, unlike dithranol, unrefined tar or phototherapy.

The only study investigating the relatively long-term use of Dovobet ran over 52 weeks in the treatment of mild to moderate psoriasis vulgaris. The study concluded that Dovobet was both tolerable and safe for this period of time.<sup>8</sup> However, again, 52 weeks falls well below the mean duration of use amongst participants in this case series.

A sensible solution to reducing the longer-term effects of Dovobet would be to determine the reasons for its misuse. One audit reported "70% of Dovobet use was not keeping with licensing recommendations".<sup>9</sup> This suggests that patients in this series are likely to be the tip of the iceberg of those in the UK misusing Dovobet.

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A potential reason for the overuse of Dovobet was highlighted by The Centre For Drug Evaluation and Research, which raised concerns that Dovobet can be easily confused with Dovonex, its constituent vitamin D analogue, which does not contain steroid. Therefore, they submitted a proprietary name review for Dovobet.<sup>10</sup> A risk assessment looked at the reconsideration of the Dovobet name. The Division of Medication Errors and Technical Support (DMETS) suggested to Leo Pharmaceuticals to remarket the brand and packaging. In response, however, Leo Pharmaceuticals objected to this idea, claiming that there was a low risk of confusion between Dovobet and Dovonex.<sup>10</sup>

By reviewing the patient consultations, it is evident that patients appreciate Dovobet's cosmetic acceptability, initial efficacy and also the perceived lack of alternatives. One study even concluded that Dovobet significantly improves the quality of life of psoriasis sufferers.<sup>11</sup> Therefore a non-messy topical treatment that benefits their psoriasis in a quick manner is appealing, and guidelines on its duration of use are disobeyed. Additionally, some patients continue to use their prescribed Dovobet in fear of developing worsening psoriasis, due to rebound side effects. The solution could be to educate patients more effectively to understand the risks of long-term Dovobet use. This could be through patient information leaflets, using nurses to educate patients and reinforcing these messages at GP consultation reviews. Further education of GPs regarding the potential side effects of Dovobet and alternative topical treatments may also be advisable.

## Conclusion

What is apparent is the need for change regarding the overuse of Dovobet. GPs and patients must be better informed to help avoid wrongly prescribing such a potent topical steroid, so as to reduce side effects. Additionally, there is a need for a long-term study addressing regular use of Dovobet, which would be much more relevant in determining the true incidence of the side effects, and the need for non-steroid-based treatments for psoriasis sufferers.

## The senior editors at the INSPIRE Student Health Sciences Research Journal



### Shashank Chaganty

Having published about my observership in rural India as part of the first INSPIRE edition, I was compelled to undertake this role as Senior Editor. Not only did this experience show me the other side of the coin, but it has also been a fantastic networking opportunity. My interaction with co-editors and authors has been memorable. In addition to being a third year medical student at Plymouth University Peninsula Schools of Medicine and Dentistry, I am President of a social-enterprise society called Enactus – this truly helps me escape the comfort of classroom theory.



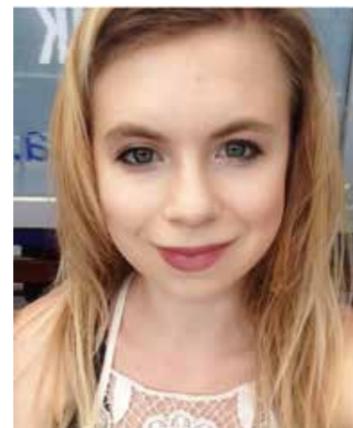
### Julia Cheong

I am a third year medical student at the University of Bristol and originally from Mauritius. I developed a keen interest in gynaecological cancer research after completing my Intercalated BSc in Biochemistry. My other areas of interest include general surgery as well as accident and emergency medicine. I hope to pursue a career in surgical oncology in the future. I am also an outdoor enthusiast and enjoy running and cycling in my spare time.



### Catarina Dores Fernandes Ferreira

Having studied an International School in Lisbon, Portugal, I moved to Bristol for university after doing a gap year volunteering in Mozambique. I am now a 5th year medical student at the University of Bristol. I intercalated in Anatomical Sciences (BSc) with first class honors, where I developed an interest for research. I have since developed a special interest in plastic and orthopedic surgery; and have been involved in a number of studies and audits around these fields.



### Lucy Hoade

I am a second year medical student at the University of Exeter. The INSPIRE scheme has connected me with some fantastic research opportunities in trauma and orthopaedics, in keeping with my interest in pursuing a future career in surgery. Outside of medicine I like to enjoy the outdoors and get out on my bicycle.



### Grace Hosking

I am a fourth year medical student at Cardiff University, currently intercalating in psychology. I have learnt a great deal in my role as Senior Editor about the process of conducting research through to publication. It has also provided opportunities to promote the INSPIRE programme and meet like-minded students from other universities. I have a wide range of research interests including paediatrics, neurology and palliative medicine.



### Amy Hough

I am a fourth year medical student at the University of Exeter and completed my clinical years in Cornwall. I have been involved with the INSPIRE programme in various roles since my second year. I am particularly interested in obstetrics and GU medicine and looking forward to pursuing this next academic year when I intercalate in a Masters in Reproductive and Sexual Health Research at the London School of Hygiene and Tropical Medicine. My personal interests include water sports, live music and cooking for friends.



### Nirmal Jayakrishnan

I am a second year medical student at Plymouth University Peninsula Schools of Medicine and Dentistry, originally from India, but living in Brunei. I've had a keen interest for research ever since researching an EPQ (Extended Project Qualification) on telemedicine, conducting environmental audits, and undertaking Special Study Units at medical school. My research interests include healthcare development, the inverse care law and general physiology. Outside of medicine, I enjoy reading and badminton.



### Alexa Korb

I am a third year medical student at Plymouth University Peninsula Schools of Medicine and Dentistry and I have thoroughly enjoyed acting as a Senior Editor for the journal over the past year. Following work experience abroad in South Africa, I have developed an interest in public health and am also drawn to anaesthetics. My interest in research has been fostered through the INSPIRE taster day scheme and I will be carrying out a hospital-based audit project locally over the summer.



### Charlie Matthias

I have recently qualified as a vet at the University of Bristol, where I also obtained an intercalated degree in cancer biology and immunology in 2015. I am particularly interested in cardiology and during my BSc, I completed a dissertation on bicuspid aortic valve, a human congenital heart condition. I thoroughly enjoyed studying a human medical condition for a change! I also took the cardiology elective during my final year. I am very interested in the charity sector, and took up a position with the PDSA (a veterinary charity) in September 2017 as a graduate veterinary surgeon.



### Toby Murray

I have just completed my medical degree at Plymouth University Peninsula Schools of Medicine and Dentistry. My interest lies in academic surgery, having completed an MSc by Research in Surgery researching the role of tryptophan in acute pancreatitis and multi-organ dysfunction syndrome. I am now working in London as an FY1 Doctor on an Academic Foundation Programme and thoroughly enjoying it!

## Acknowledgements

**INSPIRE is a national initiative  
coordinated by the Academy  
of Medical Sciences.**

**University of Bristol**

<http://www.bristol.ac.uk/medical-school/whybristol/inspire>

Leads: Tony Pickering, Reader in Neuroscience and Honorary Consultant Anaesthetist, and Elizabeth Coulthard, Consultant Senior Lecturer in Dementia Neurology

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Lead: Colin Dayan, Professor of Clinical Diabetes and Metabolism

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Leads: Prof Tamsin Ford, Professor of Child and Adolescent Psychiatry, and Joanna Tarr, Lecturer, Medical Sciences

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Leads: Vehid Salih, Reader in Oral & Dental Health Research, and David Parkinson, Professor of Neuroscience.

