Serotonin – the missing link between myocardial infarction and suicide
Acknowledgements

Thank you to RCSI Alumni for their continued support to us as students – providing career advice, acting as mentors, enabling electives, enabling research, and supporting the publication of the RCSIsmj since its inception in 2008.

We, as today’s generation of students and tomorrow’s generation of Alumni, are very grateful for this on-going support.

We would also like to thank the Dean, Professor Hannah McGee, for her sponsorship, and Margaret McCarthy in the Dean’s Office for her constant endorsement and assistance.

A special thanks to Professor Ronán M. Conroy for the time and encouragement he has given to the RCSIsmj Journal Club.

The RCSIsmj was extremely privileged to have a number of professors and clinicians involved in this year’s Journal Club. We would like to thank the following for their support of, and participation in the Journal Club, and to express our appreciation of the time, knowledge, and expertise they shared with us:

Doctor Emma Wallace
Professor Mary Cannon
Professor Arnold Hill
Professor Gerry McElvaney
Professor Ruairi Brugha
Doctor Eoghan De Barra
Professor Clive Lee
Professor Fergal O’Brien
Doctor Mary Aiken
4 Editorial
4 Director’s welcome

RCSI Ethics Challenge
5 RCSIsmj Ethics Challenge 2014/2015
6 RCSIsmj Ethics Challenge winner 2013/2014

Original articles
10 Evaluation of adverse events and patient satisfaction with day surgery before and after the implementation of pre-assessment in an Irish teaching hospital
14 Regions of atrophy that correlate with cognitive impairment in subtypes of dementia

Case reports
20 Malignant transformation of chronic ulcers (Marjolin’s ulcers): an emerging at-risk population
23 Gliosarcoma: a rare variant of glioblastoma multiforme
26 MRSA of unknown aetiology causing prostate abscess in a patient with incidental prostate adenocarcinoma

Review articles
28 Omalizumab in the treatment of severe persistent IgE-mediated asthma
33 Serotonin – the missing link between myocardial infarction and suicide
36 Rediscovering thalidomide: lessons learnt and evolving indications
41 Transvaginal cholecystectomy: a novel surgical technique
46 All in your head: is the use of placebos a form of benevolent deception?
49 Physiological mechanisms underlying exercise prescription non-compliance in patients with type 2 diabetes mellitus

Staff reviews
54 The foetal origins of adult health
58 Sleep-deprived doctors and patient safety: an unresolved link
62 Unplugging platelet function tests: reassessing the gold standard
65 Sources of, and barriers to, healthcare in armed conflicts
69 Whose life, whose death?: Pharmaceutical trials in the developing world

Perspective
73 Ensuring safe surgery for our patients – do we do enough?
77 The white coat: does it have a future in Ireland?
81 Miraculous, malevolent or misunderstood: knowledge and attitudes regarding electroconvulsive therapy

Elective report
84 Medicine and monsoons

Book review
89 The Rise and Fall of Modern Medicine by James Le Fanu

Abstract
90 Volume of caudate nucleus in major depressive disorder
The imperfection and uncertainty of medicine

“We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do.”

Atul Gawande, Complications: A Surgeon’s Notes on an Imperfect Science

With this year’s edition of the RCSIsmj, this gap narrows ever so slightly. From psychiatry to surgery, from original work to reviews of age-old practice, our pages are filled with evidence of medical progress. Javeria Tabish explores brain atrophy as a new marker for cognitive impairment in dementia, while Gurtej Singh discusses a new surgical technique for cholecystectomy. Thorough reviews examine novel theories: Nadine Straka looks at foetal origins of adult health; Michael Bravo at a physiological barrier to exercise in patients with type 2 diabetes; and, Rachel Mattson at serotonin as a link between myocardial infarction and suicide.

At the same time, articles by Amelia Reid, Elizabeth Ahern-Flynn and David Hakim speak to the very human side of medicine, and the failures – in research, practice and politics – we still face. One of the reasons I love medicine is that it is forever evolving; treatments we use regularly today were not yet developed when our parents were in medical school, and many will be obsolete by the time our children start their training. Limitations that once existed no longer do, and yet, as we progress, we meet new obstacles, previously unimagined.

It is an absolute privilege to be a medical student; the opportunities to learn and develop are endless, the room for growth expansive, and our peers are among the most innovative and compassionate. At the same time, it is a humbling experience; despite our discipline and dedication there is still so much unknown. The imperfection and uncertainty of medicine remind us of the need for continued effort and further development.

I hope that the articles in this issue spark your interest in, or help fuel a growing passion for research, and encourage you to become more involved in your education, your career, and the future of medicine. Let us aim to continue to close the gap.

Melissa Schorr
Editor-in-Chief RCSIsmj 2013-2014

Director’s welcome

It is with great pleasure that I welcome you to the seventh issue of the RCSI Student Medical Journal. Our team has put a huge amount of effort and enthusiasm into producing another high quality publication. I have every confidence that you will enjoy reading the work produced by RCSI students.

This year marks a milestone for the RCSIsmj; it is the first time that it has outlived the lifespan of a student in RCSI. Over the past seven years, the RCSIsmj has gone from strength to strength. This year, our new initiative, the student-run journal clubs, found their feet. There were very interesting presentations from leading researchers in RCSI, which sparked lively discussion among students. We were joined by another influx of enthusiastic students to the team, and we received a huge amount of excellent submissions for publication.

The RCSIsmj is an entirely student-run publication; the articles are all written by students, reviewed by their peers, and edited by them as well. The consistent high quality of the RCSIsmj is a testament to the dedication and hard work of everyone involved. I want to thank everyone who gave up their time from their busy schedules to be involved. I also want to thank the Dean’s Office in RCSI for their support and assistance, without whom this publication would not be possible.

As my four years of involvement with the RCSIsmj come to an end, I pass stewardship on to the next generation of students. I have no doubt that my colleagues will continue to grow the RCSIsmj in the future. I hope that you find the RCSIsmj serves you well – as a learning resource, a platform to publish your hard work, and a means to enter into the fascinating and important world of medical research.

“The very first step towards success in any occupation is to become interested in it.”

Sir William Osler (1849-1919), Canadian physician and founding Professor of Medicine at Johns Hopkins Hospital.

Eoin Kelleher
Director, RCSIsmj 2013-2014
The case

Ben is a 29-year-old man. He lives in the Philippines and is married with three children. He works in a factory making sports equipment. The job does not pay very well. His wife works in a shirt factory and is also poorly paid. Both of them want to ensure that their children will not have to work in factories or become migrant labourers to wealthy countries. They are aware that this can only be achieved through education. But a good education is expensive and they don’t have that kind of money. One day Ben sees the following advertisement in a local newspaper:

WANTED!
One functioning kidney to save a life!
Potential donors will be morally and financially rewarded.
Donors will receive $10,000 plus medical care.

The advertisement makes Ben think. He has two kidneys and he is healthy. He knows that donating one of his kidneys will not be without risk, but he also knows that it could potentially save someone’s life.

It would also give him enough money to pay for the education of his children so that they would not have to work in factories. It seems that everyone would benefit from the transaction.

Questions for consideration
1. Identify the ethical issues in this case.
2. What are the ethical implications of creating a market for organ donation?
3. What other methods could be introduced to increase the availability of organs for transplant?

Submission guidelines
Please construct a lucid, structured and well-presented discourse for the issues raised by this case. Please ensure that you have addressed all the questions highlighted and discuss these ethical issues academically, making sure to reference when necessary.

Your paper should not exceed 2,000 words.

Your essay will be evaluated on three major criteria:
1. Ability to identify the ethical issues raised by the case.
2. Fluency of your arguments.
3. Academic quality with regard to depth of research, appropriateness of references and quality of sources.

The winning entry will be presented with a prize at the launch of the eighth issue. Good luck!
Introduction
The 2013/2014 RCSIsmj Ethics Challenge introduces the case of 92-year-old Joan, who, per her family, is receiving medical treatment against her previously expressed wishes concerning her end-of-life care (EOLC). Despite her desire to die at home, under direction of a district nurse, Joan was removed from her home and admitted to hospital. Although her family was told that the admission would be for no longer than 48 hours, Joan is now in her fifth week as an inpatient, despite constant protest on her behalf from her family and GP. The aim of this article is to dissect the complex issue of EOLC, the ethical dilemmas highlighted by this specific case, and the need for an established practical and legal framework for EOLC in Ireland.

Core principles of medical ethics
Respect for autonomy: a patient’s right to make decisions regarding care received. If a patient’s capacity is diminished, the physician is expected to make decisions in the patient’s best interest.2,3

Beneficence: a physician’s actions should always be for a patient’s benefit and well-being.2
Non-maleficence: primum non nocere or ‘First, do no harm.’4
Justice: ‘the fair distribution of health resources’.5

Additional prima facie duties
Caring: a physician’s duty to protect, empathise with, and show concern for a patient.
Veracity: honest exchange of information as needed for the foundation of patient autonomy.6

Physicians as reflective-generative practitioners
Ethical dilemmas frequently arise “where power is concentrated and decisions are made by a single person”.7
With regard to EOLC, conflict arises when either this is the case, or when one party desires it to be so; this situation should be prevented.

Hailey Carroll BSc BA
RCSI medical student
As reflective-generative professionals, physicians should use synergic power in the doctor-patient relationship. Synergic power, as opposed to coercive power, focuses on the recognition of patients as people rather than objects. When used appropriately, this enables the doctor-patient relationship to progress to a “partnership of shared responsibility involving joint exploration” of the patient’s condition and treatment. This should take place in the context of EOLC in the following three steps:

1. As prognosis worsens, the physician’s willingness to take on the burden of making a decision with the patient should increase.
2. The preferred decision-making role of the patient and family is assessed.
3. The approach is applied to the patient’s EOLC.

Ideally, the core medical ethical principles, the additional prima facie duties, and this three-stepped approach will converge, yielding an agreed-upon EOLC plan that is ethical and optimal for the patient, relevant family members, and physician. In this case, Joan’s family and GP are not satisfied with her current EOLC. They believe her wishes are not being honoured. It is necessary to determine whether this is a breach of ethics, a result of miscommunication between those involved, or misunderstanding regarding Joan’s prognosis. Regardless, Joan’s family feels that she is a victim of coercive power. Whether or not this is true is only slightly relevant, as most importantly it highlights the need to re-establish a synergic doctor-patient relationship.

When is the ‘end of life’?

In order to aptly determine an EOLC treatment plan, ‘end of life’ as a concept must be defined. One of the most basic issues that arises in EOLC is a disagreement on this definition when the effectiveness of curative care comes into question. In order to appropriately define ‘end of life’, two important perspectives must be considered: firstly, “a disease-centred perspective based on a period of irreversible decline before death”; and secondly, “a time-based perspective”, which outlines how long this period is. The majority of legislative bodies consulted for this paper define ‘end of life’ as the three to six months preceding death, during which time the patient’s condition is “unlikely to be arrested by medical care”. Although the patient’s condition in this case is not explained clearly from a medical perspective, presuming that her described deteriorating state as a ‘skeleton of a person’ who no longer eats or drinks is accurate, it can be surmised that she is in the ‘end of life’ period from both perspectives.

Patient autonomy and capacity

The line where patient autonomy ends and physician responsibility begins is often blurred. Autonomous rights of elderly patients, especially those with dementia, can be extremely difficult to assess. In such cases, “decisions of end-of-life care often rely on statements made prior to loss of capacity; accounts from family, healthcare practitioners or care staff; and, retrospective analysis of patient records”. In the eyes of her family and GP, Joan’s wishes with regard to EOLC were explicit, and since they have been ignored, they consider her care “hijacked”. It is unclear what justifications the district nurse had for admitting Joan to hospital, but a proper assessment of her capacity and ability to make autonomous decisions would have been part of the admission process.

Curative versus palliative care

Curative care is characterised by the ability to achieve six comprehensive goals:

1. Be cured.
2. Live longer.
3. Improve or maintain function/quality of life (QoL)/independence.
4. Be comfortable.
5. Achieve life goals.
6. Provide support for family/caregiver.

When the majority of these goals are no longer realistic,
treatment transitions to palliative care. Palliative care is defined as care for patients with life-threatening conditions, but this case refers specifically to EOLC. The decision on how and when to make this transition is difficult for physicians as they struggle with "the dual responsibilities of saving lives and delivering end-of-life care". It is at this crossroads that, in fairness to the patient, treatment must be assessed in terms of both probability of survival as well as the QoL associated with survival. The transition process itself then needs to address place of care, level of care, and goals of care. In order to harmonise the wishes of the patient with the duties of the physician, a conversation, driven by caring and veracity, needs to take place. In this case, there has been an undeniable breakdown in communication during this transitional process, which will be difficult if not impossible to rectify as Joan's health declines and her family's anger grows.

Developing a framework for discussion of EOLC

The most successful, synergic, and satisfying cases of EOLC are characterised by "early communication", and identification and exploration of patients' wishes. There is a lack of a structured protocol for physicians regarding EOLC. This creates a burden on physicians regarding decisions made during EOLC. The especially fragile nature of the elderly, compounded in this case by the patient's progressing dementia, results in an end-of-life period that can be "protracted and unpredictable". This highlights the dire need for an early discussion to construct a plan for EOLC. Understandably, patients and their families may be hesitant to discuss EOLC early on in a disease diagnosis. Despite this, research shows that such a discussion "is not associated with patient distress, and is associated with a reduction in use of unsuccessful life-sustaining treatments, and improved QoL".

This discussion should include:
1. A review of the medical facts and options for EOLC.
2. Discussion of the patient's perspectives on death and dying.
3. Agreement on a care plan.
4. Discussion of the family's role in EOLC and selection of a surrogate.
5. An advanced care plan (ACP) or advanced directive (AD) when applicable.

ACPs and ADs

ACPs and ADs refer to documents that indicate a patient’s wishes regarding specific aspects of their EOLC. ACPs and ADs are supported in some healthcare systems and completely irrelevant in others. Countries such as Germany, the United States, Australia, and the United Kingdom have legislation to uphold these documents. These systems recognise that, when drafted by an autonomous patient of appropriate capacity, factors key to "dying with dignity", including symptom management and directives on prolongation of dying, can be expressed by the patient, allowing him/her to maintain a sense of choice and control in his/her own care. Some countries like Norway do not give ADs or ACPs any legal standing, which puts an undeniable strain on patient autonomy.

Legal implications

When assessing legal implications in cases pertaining to EOLC, one must consider:
1. The healthcare system in which the case takes place.
2. The patient's capacity.
3. The patient's autonomy.
5. The legislative backing in the context of an ACP or AD.
7. Physicians' decisions in the context of the principles of medical ethics.

Physicians must be confident and execute decisions regarding EOLC with a “high level of certainty”, for if they do not, the consequences they may face could be severe, whether handed down from criminal courts, legal tribunals, or licensing organisations. Many countries have court cases that have set precedents for controversial aspects, with respect to the law, of EOLC. It is suggested that if an issue does arise, a physician should seek assistance from his/her respective ethical committees as well as seeking legal counsel.

Dying with dignity

Independently, ‘dying’ and ‘dignity’ are words that lack definitional specificity. Thus, this phrase has been reassessed and redefined constantly in the context of EOLC. The American Journal of Hospice and Palliative Care defines ‘dying with dignity’ as: "Having one's human value and worth acknowledged; being cared for with respect and empathy; having a voice regarding one's dying process; minimising physical and emotional suffering; safeguarding one's privacy; maintaining emotional connection with others; resolving personal affairs; and, having access to spiritual sources of support".

Conclusion of this case

EOLC is a complex issue that presents unique challenges towards principles of medical ethics on a case-by-case basis. In looking at this case in the context of the Irish health system, certain questions need to be answered in order to assess the ethical issues in this case:

- Is Joan in the ‘end of life’ period?
- How, to whom, and when did Joan express her wishes regarding her EOLC?
- Did she have the capacity to express these wishes?
- Did she have an ACP or AD?
- Why did the district nurse see fit to move her to hospital?
Why was Joan’s family told the stay would be 48 hours maximum?

What medical treatment is she receiving as an inpatient on the ward that warrants her continued stay?

The answers to these questions will offer a better understanding of the progression of this case. However, this ambiguous case is a microcosm for EOLC in Ireland.

The lack of legislation regarding these issues only exacerbates the complexity of this case. The Irish Constitution protects a patient’s right to refuse treatment. In 2008, Judge Laffoy, when presiding over Fitzpatrick vs K, ruled that “it could not be argued that a competent adult is not free to decline medical treatment”. However, if a competent Joan had drafted an AD, confusion regarding her EOLC would still exist. The Irish Medical Council itself claims that it is “difficult to state the legal position” of ADs due to a lack of “relevant statutory provisions” in Irish legislation.

This ambiguity is unacceptable and unfortunately allows Joan’s experience with EOLC in the Irish system to be an example of diminished dignity while dying simply due to a lack of protocol. Perhaps it is not only the doctor-patient relationship that needs to value synergic power, but also the relationship between the Irish Medical Council and its constituents.

References

Evaluation of adverse events and patient satisfaction with day surgery before and after the implementation of pre-assessment in an Irish teaching hospital

Abstract
Objectives: Advancements in surgical techniques have facilitated the rapid expansion of day surgical services. In 2011, a study was carried out to evaluate patients’ satisfaction with the day surgery process and their experience of adverse events. Based on the findings, a nurse-led pre-assessment process was introduced as part of the development of best practice for day surgery in Ireland. Subsequently, this study was carried out in 2013 for re-evaluation of patient satisfaction and adverse events.

Methods: The study design was a telephone questionnaire. Patients who had undergone nurse pre-assessment since November 2012 were given full information before being invited to participate in the survey. Data collection was completed in July 2013.

Results: Of the 150 patients, 91 were eligible and completed the survey (60.67%). The data was compared with 2011 data. Patients were satisfied overall with the implementation of the pre-assessment process. Although adverse events increased over time, unplanned return visits decreased in the 2013 cohort.

Conclusion: Clear communication before and after a procedure is vital to prevent unnecessary return visits. The pre-assessment process helps in providing clarification and reassurance to patients. Multidisciplinary collaboration is crucial to maintain a high level of patient satisfaction.

Key words: Day surgery; pre-assessment; patient satisfaction; adverse event; return visit.
Introduction

The Health Service Executive (HSE) defines a day case as a hospital admission “on an elective basis for care and/or treatment, which does not require the use of a hospital bed overnight and who is discharged as scheduled”. Ongoing development of surgical techniques and short-acting anaesthesia allows certain procedures to be performed as day cases. Day surgery (DS) has several advantages, including short-term hospital stay, faster recovery due to minimal invasiveness, and cost reduction for the patients attending the hospital. This leads to a more consumer-friendly treatment. According to a report by the World Health Organisation (WHO), Canada and the US now expect 90% of elective procedures to be carried out as DS. The UK and Scandinavian countries are also dedicated to increasing DS levels. In Ireland, however, DS uptake is still relatively low, although the HSE aims to increase the current rate of 55% to 80%. The relatively low numbers of DS procedures in Irish hospitals have resulted in a paucity of data on certain aspects of the process. Starting in 2011, a three-year project to improve the DS service in Ireland was commenced. One of the aspects of the study was to measure patients’ satisfaction and adverse events associated with DS. Through this study, high rates of unplanned return visits postoperatively were discovered. These were due to various adverse events such as fatigue, drowsiness, poor appetite, and sore throat. Steamming from this research, a set of guidelines called the ‘Best Practice Statements on Day Surgery in Ireland’ were developed. These include patient information leaflets (PILs), pre-assessment, documentation, management, discharge and monitoring.

The aim of this study was to verify patients’ satisfaction, and to quantify and qualify adverse events following DS in an Irish teaching hospital, and to compare these findings with those from the initiation of nurse-led pre-assessment and of the ‘Best Practice Statements for Day Surgery’ in 2011.

Methods

The study design was a cross-sectional survey, using a telephone questionnaire. All patients attending for DS between November 2012 and June 2013 inclusive, underwent pre-assessment with a nurse. All pre-assessed patients were invited to participate in the survey. Patients were fully informed, assured of confidentiality, and made aware of their right to opt out of the study at any time. Patients who agreed to participate received a telephone call during a pre-arranged date and time. The questionnaire was designed taking the 2011 study into consideration. Construct validity was ensured through review of the questionnaire by personnel involved in DS (chief nurse, research nurse, consultant anaesthetist and consultant surgeon). Pilot testing was completed and no further revisions were made. The completed questionnaire contained 27 questions to evaluate five areas of the DS process. The questions were generally closed, requiring a ‘yes’, ‘no’ or ‘don’t know/don’t remember’ answer. Additional open questions were asked to allow patients to give qualitative answers. All data was analysed using Microsoft Excel. The study was approved by the hospital’s Research Ethics Committee.

Results

A total of 150 patients were pre-assessed by the nurse prior to DS between November 2012 and June 2013. Of these, 36 (24%) patients were not eligible for the study as their surgery was not performed for various reasons. The remaining 114 eligible patients were contacted by phone in July 2013, and 102 (89.5%) responded. After contact had unsuccessfully been attempted three times, 12 patients (10.5%) were deemed unresponsive and not included in the study. Of the 102 patients who did respond, 11 (10.8%) did not complete the survey. Reasons included: patient declined participation; phone was not in service; patient did not speak English; family bereavement; patient was deaf; and, patient was transferred to another hospital. Therefore, 91 (79.8%) patients out of 114 eligible patients completed the survey (Table 1).

Patient information leaflet

Of the 91 patients included in the study, 85 (93.4%) received a PIL regarding their procedure, of which 81 (95.3%) reported actually having read it. In 38 (44.71%) cases, both the patient and the patient’s carer read the leaflet. Forty-nine patients (53.9%) referred to a secondary source for more information regarding the procedure (Figure 1).

Table 1: Patient demographics of three survey studies.

<table>
<thead>
<tr>
<th>Patient satisfaction (2011)*</th>
<th>Adverse events (2011)*</th>
<th>Patient satisfaction and adverse events in patients that were nurse pre-assessed (2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible patients</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td>Completed survey</td>
<td>60</td>
<td>83</td>
</tr>
<tr>
<td>Patient response rate</td>
<td>85.7%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Male: female ratio</td>
<td>24:36</td>
<td>29:54</td>
</tr>
<tr>
<td>Patient mean age</td>
<td>47 years</td>
<td>46 years</td>
</tr>
</tbody>
</table>

*Data from the initial surveys carried out by the research team in 2011.
Unplanned return to healthcare clinic post operatively
A total of 23 patients (25%) had an unplanned return to a healthcare service provider following surgery (Figure 2). Overall, seven (7.7%) patients had an unplanned visit to the hospital following DS. The reasons for their returns were: pain (n=3); symptoms of infection (n=2); swelling (n=1); and, need for colonoscopy (n=1). The time period between surgery and unplanned return ranged from four days to four weeks. Three of the seven patients were reassured by staff and required no additional management. In total, 15 (16.5%) patients had an unplanned visit to their GP. One (1.1%) patient returned to the practice nurse after DS. The reasons for their returns were: pain (n=4); weight loss and fatigue (n=3); undissolved stitches (n=3); swelling (n=2); symptoms of infection (n=2); leakage from the surgical site (n=1); and, allergic reaction to bandages (n=1). The time between surgery and return visits ranged from two days to 10 weeks, with a peak between one and two weeks post operatively (n=6). Most patients were managed by the GP or practice nurse; however, six (37.5%) were referred to the hospital. Additionally, 10 (11%) patients phoned the Day Surgery Unit (DSU), mainly with regard to wound healing.

Adverse events

Pain
Sixty-seven patients (76.3%) experienced some form of pain after being discharged (Figure 3). Most patients’ pain was at the surgical site or was wound specific (n=64; 95.5%). Pain severity on a scale of 1 to 10 (10 being the worst pain ever) was evenly distributed across the scale with a mode of 6. Pain duration varied greatly from a few hours (n=6; 9%) to persisting (n=12; 17.9%). Of the 63 patients who took pain relief tablets, 54 (85.7%) experienced full relief with no side effects. Six patients had no pain relief and the other three experienced side effects. Thirteen patients achieved pain relief by other conservative means. Of the 67 patients who reported postoperative pain, 27 (40.3%) reported that their lifestyle was affected due to the pain, with negative impacts on sleeping, eating, mobility, and ability to go to work.

Nausea and vomiting
Eleven patients (12%) reported nausea, vomiting or both after discharge; eight patients reported disruption in sleep and eating as a result.

Comparison to 2011
The results of this study compared to the results from the 2011 study are outlined in Figures 1, 2 and 3. Overall distribution of PILs increased
(from 87.95% to 93.4%), and they were read by more families (from 29% to 44.7%) from 2011 to 2013. However, there was also an increase in referral to a secondary source for information, from 21.7% in 2011 to 53.9% in 2013. Unplanned return visits decreased overall from 2011 to 2013, with 7.7% returning to hospital in 2013 compared to 10.8% in 2011, and 16.5% returning to the GP compared to the previous 26.5%. Interestingly, adverse events increased from 2011 to 2013 over all four outcomes: drowsy/tired; sore throat; poor sleep/appetite; and, pain/discomfort.

Discussion and conclusion

As the study is still in the initial stages of implementing ‘Best Practice Statements on Day Surgery in Ireland’, and looks at only one aspect, it is hard to draw conclusions about the guidelines as a whole. However, it is interesting to compare differences between the surveys carried out initially in 2011, and this current one. The number of patients provided with an appropriate PIL remained high. However, the 2013 survey showed an increased number of referrals to secondary sources for further information. This may suggest that the leaflet does not provide sufficient information. The research team is currently working to improve the PILs for both hard copy and online versions. Overall, there has been increased reporting of adverse events over time. This may be explained by the different time frame in which the survey was carried out. The 2011 survey was carried out three weeks post operatively, whereas the 2013 survey was carried out from three weeks to six months post operatively, covering both immediate and long-term adverse events.

A study reports that the discomfort and other adverse events that patients experience may last up to three months post surgery. However, this increase in adverse events must be evaluated taking into account the number of patients who returned to a health service provider as a result of these adverse events. Despite the higher rate of adverse events, the 2013 report showed a lower rate of unplanned return visits. This may be a result of pre-assessment. The nurse in charge took approximately 20 minutes with each patient to go through all the details involved in the procedure, thereby better informing the patients and providing reassurance with regard to possible side effects of the procedure. This may have prevented patients from unnecessarily seeking advice from a healthcare professional.

A national survey carried out in Ireland in 2010 reported return admission rates ranging from 0.3% to 9.5%, with the majority less than 3%. Unanticipated hospital admission rate reported at the annual scientific meeting in Glasgow in 2006 was also 1-2%. Although none of the patients in this study who returned to hospital were admitted, there is still room to improve on adverse events in patients that lead to unplanned return visits.

Clear communication before and after a procedure is vital to provide clarity to patients and to reassure them regarding the post-operative course and management, and to prevent unnecessary return visits. This current study adds to our knowledge of adverse events both short and long term, and how pre-assessment may be an effective way of preventing unnecessary healthcare facility visits, and therefore reducing healthcare costs and waiting lists.

Acknowledgements

This study forms part of a larger Health Research Board (HRB) funded study to develop best practice for the provision of day surgery in Ireland (Professor S. Cowman, Principal Investigator). The student was funded by the HRB grant, finance code 1319.

References


Regions of atrophy that correlate with cognitive impairment in subtypes of dementia

Abstract

Objectives: The objective of this study was to examine regions of volume loss in the different subtypes of dementia to find novel biomarkers for diagnosis of the disease in vivo.

Methods: Sixty-three computed tomography (CT) scans of patients with diagnoses of mild cognitive impairment (MCI, n=17), Alzheimer’s disease (AD, n=15), vascular cognitive impairment (VCI, n=21) and vascular dementia (VaD, n=10) were obtained from the memory disorders clinic at St Michael’s Hospital, Toronto. In addition to cognitive evaluation carried out using the Behavioural Neurology Assessment (BNA), all patients underwent a CT scan. Linear measurements were performed to assess degree and location of atrophy and then correlated with the BNA.

Results: Patients with MCI showed significant loss of volume in the temporal horn (p<0.01), suprasellar cistern (p<0.05) and frontal (p<0.05) regions which correlated with declining memory. Patients with AD displayed significant loss of temporal horn volume (p<0.01) and third ventricle regions (p<0.05), which correlated with memory loss. Patients with VCI displayed decreased volume in the suprasellar cistern (p<0.01), bicaudate (p<0.05) and third ventricle (p<0.05) regions, which correlated with memory loss. Similar correlations in the suprasellar cistern (p<0.01) and bicaudate (p<0.05) regions were found in VaD, in addition to volume loss in frontal (p<0.05) regions, which correlated with declining executive function.

Conclusion: Although the pattern of atrophy seen with MCI and AD patients was as expected, new regions of volume loss were found in patients with VCI. The existence of atrophy in the bicaudate region is a novel finding for this diagnosis, as atrophy was previously suspected in more frontal regions. This implies that volume loss in the bicaudate region can be used as a biomarker when correlated with memory to predict conversion from VCI to VaD.
Introduction
Alzheimer's disease (AD) and vascular dementia (VaD) are the two most prevalent forms of dementia worldwide. Although these two diseases have different aetiologies, both result in devastating health implications for the individual, socio-economic impositions on the caregiver, and a staggering worldwide annual cost of US$604 billion. The clinical hallmark of AD is amnestic deficit prior to cognitive decline that affects all other cognitive domains. Clinical manifestation of VaD, by contrast, is dependent on the anatomical location of the vascular insults. Interestingly, both of these forms of dementia may be the end result of a progressive syndrome of impairment in one or more cognitive domains that does not cause functional impairment. Mild cognitive impairment (MCI) is a recognised prodromal stage of AD, and though vascular cognitive impairment (VCI) serves as an 'umbrella term' for multiple other cerebrovascular dementias, a VCI diagnosis can also precede one of VaD. AD is a neurodegenerative disease, involving beta amyloid plaque formation and tau-containing neurofibrillary tangles. VaD reflects a more dynamic disease. It can result from a variety of cerebrovascular disorders including haemorrhagic or ischaemic brain damage. The subsequent clinical features and therapeutic interventions vary for each disease; however, it is essential to distinguish between the subsets of dementia in the early stages of diagnosis. Although the course of functional decline in both diseases – gradual in Alzheimer's compared to a stepwise decline typically seen in VaD – helps clinicians to make a diagnosis, an earlier marker that appears before significant impairment is key. Neuroimaging studies at present focus on identifying in vivo biomarkers to enable earlier diagnosis, and monitor disease progression and therapeutic effect. Numerous structural magnetic resonance imaging (MRI) studies on AD have reported significant atrophy of structures in the medial temporal lobes and in the temporo-parietal association areas. Imaging studies of patients with VaD, however, seldom focus on atrophic change, and more commonly show multiple or significant single infarcts, haemorrhages, multiple lacunes and white matter lesions. Memory is initially and most severely affected in AD, compared to a stepwise decline typically seen in VaD – helps clinicians to make a diagnosis, an earlier marker that appears before significant impairment is key. Insult to the frontal or pre-frontal areas of the brain can impair executive functioning and have detrimental effects on ability to make plans, verbal reasoning, inhibition, and mental flexibility. A review of the scientific literature indicates that substantial research has been carried out using MRI measures of disease progression. However, studies using computed tomography (CT) are limited even though CT is the most prevalent form of neuroimaging for patients referred to memory clinics. The ability to identify patients who are likely to progress from MCI to AD and VCI to VaD using simpler methods than MRI analysis is invaluable. The present study uses linear measurements as described by Zhang et al. to measure regional cerebral atrophy and correlate this data with the different cognitive domains outlined by the Behavioral Neurology Assessment (BNA).

The BNA is a neuropsychiatric assessment tool used most commonly in hospitals and clinics in the Greater Toronto Area. It is a quick measure (<20 minutes) of the degree of cognitive impairment (sensitivity of 93%, specificity of 93%) in patients with suspected dementia. The aim of this study is to use those diagnostic methods routinely used in memory clinics to find novel biomarkers for the diagnosis of dementia and establish methods to differentiate AD from VaD earlier in the course of the disease.

Methods
Participants
Scans of 63 patients with diagnoses of MCI, AD, VCI and VaD were obtained from the memory disorders clinic at St Michael’s Hospital in Toronto, Canada. Prior to a CT scan, all patients were evaluated via history, physical examination and cognitive function evaluations, including the Mini Mental State Exam (MMSE) (total score out of 30) and BNA (total score out of 114). The BNA includes measures of memory, language, attention, visuospatial function, naming and executive function; a higher score indicates more cognitive impairment, whereas a lower score on the MMSE signifies a greater decline. AD and VaD patients were matched by age, BNA and MMSE scores (see Table 1). The same was done for MCI and VCI patients. All patients spoke English as a first language. This study received approval from the hospital’s Research Ethics Board.

CT acquisition
All participants underwent non-contrast axial cranial CT. The following parameters were used: 120Kv at 2.5mm and 5mm slice thickness with a range of 170-340mA at 2.5mm slice thickness and 140-280mA at 5mm slice thickness.

CT measurements
Linear measurements were taken using the digital calipers in Analyze 9.0. The rater was blinded to the participants’ clinical data. The following seven linear measurements deemed statistically significant by Zhang et al. were used: maximal transverse intracranial width (A); maximal width of the frontal skull (B); maximal width of the third ventricle (C); minimal intercaudate difference (D); maximal frontal horn width (E); suprasellar cistern (F); and, temporal horn diameter (derived from averaging the left and right temporal horn diameters) (G). Using these measurements, the following indices and ratios were calculated: third ventricle ratio (C/A); bicaudate ratio (D/A); Evans

Table 1: Demographic and cognitive values of AD and VaD patients.

<table>
<thead>
<tr>
<th></th>
<th>AD (n=15)</th>
<th>SD</th>
<th>VaD (n=10)</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at CT scan</td>
<td>77.7</td>
<td>6.2</td>
<td>76.2</td>
<td>8.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Overall BNA (/114)</td>
<td>66.5</td>
<td>14.4</td>
<td>63</td>
<td>14.4</td>
<td>0.56</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>22.2</td>
<td>3.7</td>
<td>24.3</td>
<td>4</td>
<td>0.20</td>
</tr>
</tbody>
</table>

RCSI

original article

smj

original article

Volume 7: Number 1. 2014 | Page 15
ratio (E/B); Huckman’s number (D+E); suprasellar cistern ratio (F/A); and, temporal horn ratio (G/A) (Figure 1).19

Statistics
A one-tailed bivariate correlation (where r=Pearson’s coefficient) was used when a decreasing BNA domain was hypothesised to increase the CT ratios. A two-tailed correlation was used when the nature of the relationship could not be predicted.

Results
Demographic data of the four diagnostic groups is outlined in Tables 1 and 2. When compared to their cognitive counterpart, there were no statistically significant differences between groups in age at CT, total BNA or total MMSE score, as all p-values were >0.10. Tables 3 and 4 compare the means of the BNA subsets within groups that share the same aetiology, i.e., MCI with AD and VCI with VaD. P-values were <0.05, with the exception of attention and concentration, across VCI and VaD.

Table 2: Demographic and cognitive values of MCI and VCI patients.

<table>
<thead>
<tr>
<th></th>
<th>MCI (n=17)</th>
<th>VCI (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at CT scan</td>
<td>69.1</td>
<td>70.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Overall BNA (/114)</td>
<td>89.1</td>
<td>89.3</td>
<td>0.94</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>27.8</td>
<td>27.4</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Table 3: Measures of the BNA subsets of AD and MCI patients.

<table>
<thead>
<tr>
<th></th>
<th>AD (n=15)</th>
<th>MCI (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and concentration</td>
<td>1.87</td>
<td>4.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Memory</td>
<td>16.53</td>
<td>21.41</td>
<td>0.00086</td>
</tr>
<tr>
<td>Naming</td>
<td>17.33</td>
<td>22.76</td>
<td>0.0022</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>11.27</td>
<td>13.12</td>
<td>0.019</td>
</tr>
<tr>
<td>Executive function</td>
<td>19.53</td>
<td>27.59</td>
<td>0.00076</td>
</tr>
</tbody>
</table>

Table 4: Measures of the BNA subsets of VaD and VCI patients.

<table>
<thead>
<tr>
<th></th>
<th>VaD (n=10)</th>
<th>VCI (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and concentration</td>
<td>2.9</td>
<td>3.67</td>
<td>0.15</td>
</tr>
<tr>
<td>Memory</td>
<td>16.6</td>
<td>22.86</td>
<td>0.00041</td>
</tr>
<tr>
<td>Naming</td>
<td>16.4</td>
<td>22.29</td>
<td>0.00062</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>11.4</td>
<td>13.71</td>
<td>0.013</td>
</tr>
<tr>
<td>Executive function</td>
<td>15.5</td>
<td>26.81</td>
<td>0.00068</td>
</tr>
</tbody>
</table>
Table 5: Bivariate correlation of CT measures and the cognitive domains of the BNA in 17 MCI patients.

<table>
<thead>
<tr>
<th>MCI</th>
<th>Suprasellar ratio</th>
<th>Temporal horn ratio</th>
<th>Bicaudate ratio</th>
<th>Huckman's number</th>
<th>Third ventricle ratio</th>
<th>Evans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and concentration</td>
<td>0.024</td>
<td>0.093</td>
<td>0.065</td>
<td>0.116</td>
<td>0.118</td>
<td>-0.054</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.928</td>
<td>0.724</td>
<td>0.806</td>
<td>0.658</td>
<td>0.652</td>
<td>0.838</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.421*</td>
<td>-0.606**</td>
<td>-0.23</td>
<td>-0.514*</td>
<td>-0.110</td>
<td>-0.358</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.046</td>
<td>0.01</td>
<td>0.19</td>
<td>0.017</td>
<td>0.337</td>
<td>0.079</td>
</tr>
<tr>
<td>Naming</td>
<td>-0.216</td>
<td>-0.457</td>
<td>-0.386</td>
<td>-0.386</td>
<td>-0.223</td>
<td>-0.241</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.406</td>
<td>0.056</td>
<td>0.126</td>
<td>0.126</td>
<td>0.39</td>
<td>0.352</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>-0.234</td>
<td>-0.103</td>
<td>-0.089</td>
<td>-0.088</td>
<td>-0.178</td>
<td>-0.249</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.366</td>
<td>0.694</td>
<td>0.734</td>
<td>0.736</td>
<td>0.494</td>
<td>0.336</td>
</tr>
<tr>
<td>Executive function</td>
<td>-0.066</td>
<td>-0.062</td>
<td>-0.398</td>
<td>-0.359</td>
<td>-0.156</td>
<td>-0.274</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.400</td>
<td>0.407</td>
<td>0.057</td>
<td>0.079</td>
<td>0.275</td>
<td>0.144</td>
</tr>
</tbody>
</table>

Table 6: Bivariate correlation of CT measures and the cognitive domains of the BNA in 15 AD patients.

<table>
<thead>
<tr>
<th>AD</th>
<th>Suprasellar ratio</th>
<th>Temporal horn ratio</th>
<th>Bicaudate ratio</th>
<th>Huckman's number</th>
<th>Third ventricle ratio</th>
<th>Evans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and concentration</td>
<td>-0.319</td>
<td>-0.226</td>
<td>-0.400</td>
<td>-0.247</td>
<td>-0.425</td>
<td>0.190</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.268</td>
<td>0.416</td>
<td>0.140</td>
<td>0.374</td>
<td>0.114</td>
<td>0.498</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.044</td>
<td>-0.655**</td>
<td>-0.318</td>
<td>-0.299</td>
<td>-0.468*</td>
<td>0.022</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.438</td>
<td>0.004</td>
<td>0.124</td>
<td>0.139</td>
<td>0.039</td>
<td>0.469</td>
</tr>
<tr>
<td>Naming</td>
<td>-0.275</td>
<td>-0.207</td>
<td>-0.234</td>
<td>-0.232</td>
<td>-0.288</td>
<td>0.105</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.320</td>
<td>0.458</td>
<td>0.408</td>
<td>0.406</td>
<td>0.298</td>
<td>0.71</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>-0.064</td>
<td>0.147</td>
<td>0.286</td>
<td>0.297</td>
<td>0.486*</td>
<td>0.096</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.822</td>
<td>0.602</td>
<td>0.302</td>
<td>0.282</td>
<td>0.066</td>
<td>0.734</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.381</td>
<td>-0.022</td>
<td>-0.177</td>
<td>-0.108</td>
<td>-0.205</td>
<td>0.144</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.081</td>
<td>0.469</td>
<td>0.264</td>
<td>0.351</td>
<td>0.232</td>
<td>0.304</td>
</tr>
</tbody>
</table>

Table 7: Bivariate correlation of CT measures and the cognitive domains of the BNA in 21 VCI patients.

<table>
<thead>
<tr>
<th>VCI</th>
<th>Suprasellar ratio</th>
<th>Temporal horn ratio</th>
<th>Bicaudate ratio</th>
<th>Huckman's number</th>
<th>Third ventricle ratio</th>
<th>Evans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and concentration</td>
<td>-0.056</td>
<td>0.362</td>
<td>0.091</td>
<td>0.266</td>
<td>0.307</td>
<td>0.311</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.808</td>
<td>0.106</td>
<td>0.696</td>
<td>0.244</td>
<td>0.176</td>
<td>0.170</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.484**</td>
<td>-0.32</td>
<td>-0.479**</td>
<td>-0.214</td>
<td>-0.414*</td>
<td>-0.020</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.01</td>
<td>0.08</td>
<td>0.049</td>
<td>0.176</td>
<td>0.031</td>
<td>0.466</td>
</tr>
<tr>
<td>Naming</td>
<td>-0.220</td>
<td>0.121</td>
<td>0.078</td>
<td>0.083</td>
<td>-0.111</td>
<td>-0.068</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.338</td>
<td>0.602</td>
<td>0.738</td>
<td>0.720</td>
<td>0.634</td>
<td>0.770</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>0.188</td>
<td>-0.051</td>
<td>-0.004</td>
<td>-0.071</td>
<td>-0.036</td>
<td>0.012</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.414</td>
<td>0.828</td>
<td>0.986</td>
<td>0.760</td>
<td>0.878</td>
<td>0.960</td>
</tr>
<tr>
<td>Executive function</td>
<td>-0.227</td>
<td>0.052</td>
<td>-0.095</td>
<td>-0.114</td>
<td>0.009</td>
<td>0.019</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.161</td>
<td>0.411</td>
<td>0.341</td>
<td>0.311</td>
<td>0.484</td>
<td>0.468</td>
</tr>
</tbody>
</table>

Table 8: Bivariate correlation of CT measures and the cognitive domains of the BNA in 10 VaD patients.

<table>
<thead>
<tr>
<th>Vascular dementia</th>
<th>Suprasellar ratio</th>
<th>Temporal horn ratio</th>
<th>Bicaudate ratio</th>
<th>Huckman's number</th>
<th>Third ventricle ratio</th>
<th>Evans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and concentration</td>
<td>0.042</td>
<td>0.285</td>
<td>0.005</td>
<td>-0.582</td>
<td>0.338</td>
<td>-0.515</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.908</td>
<td>0.424</td>
<td>0.988</td>
<td>0.078</td>
<td>0.340</td>
<td>0.128</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.806**</td>
<td>0.238</td>
<td>-0.652*</td>
<td>-0.153</td>
<td>-0.267</td>
<td>0.230</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.002</td>
<td>0.254</td>
<td>0.021</td>
<td>0.337</td>
<td>0.228</td>
<td>0.261</td>
</tr>
<tr>
<td>Naming</td>
<td>-0.315</td>
<td>0.446</td>
<td>-0.495</td>
<td>-0.144</td>
<td>0.338</td>
<td>0.011</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.376</td>
<td>0.196</td>
<td>0.146</td>
<td>0.692</td>
<td>0.34</td>
<td>0.976</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>-0.387</td>
<td>0.297</td>
<td>-0.136</td>
<td>-0.584</td>
<td>0.320</td>
<td>-0.459</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.27</td>
<td>0.406</td>
<td>0.708</td>
<td>0.076</td>
<td>0.366</td>
<td>0.182</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.097</td>
<td>0.166</td>
<td>-0.254</td>
<td>-0.604*</td>
<td>0.066</td>
<td>-0.676*</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.395</td>
<td>0.323</td>
<td>0.240</td>
<td>0.032</td>
<td>0.428</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level.
*Correlation is significant at the 0.05 level.
The results obtained from the CT measurements and their BNA correlates are shown in Tables 5 to 8 for each diagnostic group. The strongest correlation for patients with MCI was seen when correlating memory with the temporal horn ratio (p<0.01), suprasellar cistern ratio (p<0.05) and Huckman's number (p<0.05). Memory in patients with AD correlated with the temporal horn ratio (p<0.01) and third ventricle ratio (p<0.05). Patients with VCI displayed strong correlations between memory and the suprasellar cistern ratio (p<0.01), the bicaudate ratio (p<0.05) and the third ventricle ratio (p<0.05). Similar correlations with memory and the suprasellar cistern ratio (p<0.01) and bicaudate ratio (p<0.05) were found in VaD, in addition to correlations of executive function with Huckman's number (p<0.05) and Evans ratio (p<0.05).

Discussion
In this study, simple CT measures were used to compare regions of atrophy and the areas of cognition they affected in four diagnostic groups. AD was matched with VaD and MCI with VCI on the basis of demographic and cognitive data to allow accurate comparisons between the two pathologies. Additionally, to demonstrate that MCI and VCI patients had less cognitive impairment than AD and VaD patients across all cognitive domains, the means of the BNA subsets were calculated and compared. These two comparative measures were done to further validate the subsequent correlation analysis.

Regions of atrophy
A pattern of atrophic change is clearly visible when looking at CT ratios of MCI and AD patients. Memory is the only cognitive domain affected in both diagnostic groups, though the correlation with the temporal horn ratio is much stronger in AD than in MCI. This finding is consistent with previous studies, as the temporal horn ratio is the most indicative of AD pathology when compared to the other ratios. Furthermore, this suggests an acceptable sensitivity of using CT linear measurements in conjunction with the BNA, as similar results of regions of atrophy in MCI and AD are widely accepted. Interestingly, memory is the only domain that correlated with the CT ratios, specifically the bicaudate ratio, in VCI patients. This pattern is also seen in VaD (though the correlations are stronger), in addition to the expected correlation of executive function with the ratios that indicate frontal atrophy. This finding suggests that memory change associated with the bicaudate ratio is most predictive of disease progression from VCI to VaD, and that frontal dysfunction occurs later on in the disease. This study is the first to establish this new marker to predict conversion to VaD and distinguish it from AD.

The caudate nucleus and the future
Although the suprasellar cistern is associated with memory loss, the bicaudate ratio is not; this warrants the question of what specific anatomical structures, which contribute to the bicaudate ratio, are affected. An MRI volumetric study by Looi et al. explores caudate nucleus volumes in control, stroke and VaD patients. They hypothesised that cerebrovascular disease contributes to caudate nucleus atrophy, which in turn disrupts fronto-subcortical circuits. Although atrophy of this structure increased from the control group to stroke and VaD patients, the study did not compare VaD patients with any other subtypes of dementia, making this measure sensitive but not specific. Looi and colleagues do, however, provide some insight to our findings. If the caudate nucleus is affected in the early stages of vascular cognitive impairment, then perhaps progressive atrophy of this structure may lead to the pathognomonic frontal dysfunction in VaD via association areas and circuits. Further studies should be conducted on caudate nucleus volume in relation to the different dementia subtypes, especially as all forms of dementia have such different aetiologies. Comprehensive MRI measures – both structural and functional – should be conducted to examine precise anatomical subregions of atrophy within the bicaudate region. Additionally, future studies should use more extensive neuropsychiatric batteries, as the BNA is a relatively quick measure used in the interest of time in memory clinics. Currently, CT is used more as a screening measure to exclude causes of secondary dementias such as haematomas, hydrocephalus and neoplasms. However, in light of these new findings, it is worthwhile to analyse linear measurements for patients referred to the memory clinic with cardiovascular risk factors. Once those patients at risk of developing VaD have been identified, aggressive management of cardiovascular risk factors as well as cholinergic treatments – which show great promise when implemented early – can commence.

Limitations
Limitations of this study include an absence of an education and occupation measure. The four diagnostic groups are not comparable on the basis of education – for many, higher education increases baseline function, which can appear to delay the onset of dementia. In addition, further investigation on the location of the vascular insults in VCI and VaD to look for whether the infarcts are clustered or evenly distributed is needed. Once the anatomical locations are documented, hypotheses on why the atrophic change occurred within the particular regions can be formed.

Conclusion
This study affirms and expands upon findings of atrophic change in the conversion of MCI to AD, and provides a novel marker of atrophic change in the conversion of VCI to VaD. Linear measurements performed on CT, together with the BNA, have established that atrophy of the bicaudate region is a novel diagnostic method and a discriminant between the early forms of the two most common forms of dementia. As both CT scans and cognitive tests are frequently used in memory clinics, the simple measures used here can be easily reproduced in a memory clinic setting and act as a new diagnostic marker. Early identification of at-risk individuals will allow treatment to begin before significant functional impairment occurs.
References
Malignant transformation of chronic ulcers (Marjolin’s ulcers): an emerging at-risk population

Abstract
Children born with neural tube defects (NTDs) have significant high morbidity and mortality rates. Myelomeningocele is a form of NTD that causes severe neurological deficits. Other serious complications can arise from poor adaptation to these resulting deficits. Preventive measures and proper management are essential to improve healthcare outcomes, and to reduce health and financial burdens on both individuals and society.

A 30-year-old Kenyan gentleman presented to the hospital with chronic, painful, non-healing gluteal ulcers. He had a background history of congenital myelomeningocele, with resulting paraplegia and incontinence. A biopsy of the lesion showed areas of squamous cell carcinoma (Marjolin’s ulcers). This was believed to have resulted from life-long abnormal mobility techniques, leading to chronic ulceration and inflammation of the gluteal region; the patient used his arms to slide his bottom across the floor, as he could not afford a wheelchair. His management plan included a wide excision of the tumour followed by skin grafting. A loop colostomy had to be performed prior to surgery to allow for proper wound healing, counselling and follow-up were also required.

Chronic inflammation, chronic wounds and scars are all predisposing factors in the development of Marjolin’s ulcers. Marjolin’s ulcers are an aggressive form of squamous cell carcinoma that requires immediate surgical intervention. The incidence of Marjolin’s ulcers is increasing in Africa due to an increase in the survival rate of babies born with NTDs; thus, health education for patients with regard to ulcer prevention and treatment should be advocated by healthcare professionals.
Introduction

Malignant transformation of chronic wounds is rare and often misdiagnosed. Sites of chronic inflammation, chronic wounds and scars are all susceptible to malignant transformation into squamous cell carcinoma (SCC); this form of SCC may present as chronic skin ulceration that fails to heal spontaneously or with appropriate therapy. The term Marjolin’s ulcer is used to refer to SCC arising from chronically inflamed skin lesions.\(^1\) Delay in diagnosis of Marjolin’s ulcers may result in a poor prognosis. Marjolin’s ulcers are uncommon but aggressive tumours. They have a high rate of local recurrence and lymph node metastases, and often require immediate surgical intervention with wide margin excision and lymph node dissection.

There is a wide variation in the interval between the initial skin damage and the appearance of the tumour; SCC can appear any time between six weeks and 60 years after the initial traumatic event.\(^2,3\)

Case report

This is the case of a 30-year-old Kenyan gentleman who presented to the Rift Valley Provincial General Hospital in Nakuru, Kenya, complaining of longstanding, painful, multiple gluteal ulcerations. He had a background history of congenital myelomeningocele, which led to arrested hydrocephalus, paraplegia, incontinence and mild learning difficulties.

The initial diagnosis was chronic deep pressure sores (grade four) based on the patient’s history of longstanding compromised mobility, and he was managed accordingly. After two weeks of antibiotics and daily wound cleaning and dressing, the ulcerations had not improved, so he was admitted again, and skin debridement and biopsy under general anaesthesia were performed.

The histopathology report showed the following: Macroscopic findings included multiple hard, isolated and fungating skin nodules on the sacrum (10cm), left gluteal region (15cm) and right gluteal region (10cm). The skin showed desquamation and ‘watery appearance’. There were no features of infection. Microscopic findings included some areas of moderate to poorly differentiated SCC arising from surface dysplasia. Other areas showed extensive parakeratosis and pseudoepitheliomatous hyperplasia. No lymphovascular invasion was seen. These findings are consistent with moderate to poorly differentiated keratinising SCC.

Detailed personal and collateral histories revealed a long history of abnormal mobility pattern adopted by the patient since childhood, as his parents could not afford to buy a wheelchair. The patient learned to move around using his arms to drag his buttocks across the floor. The repetitive trauma to the sacral and gluteal epithelium led to chronic ulcerations that had undergone malignant transformation into SCC over 30 years. He required a wide excision of the malignant lesion, followed...
by skin grafting. A loop colostomy needs to be performed prior to the main surgery to allow for proper wound healing, as the patient has suffered from urine and bowel incontinence since birth. These procedures have not yet been carried out however, because the patient cannot afford the surgical fees. He has been kept in the hospital for several months while attempting to raise money to pay the fees.

Hospital policy requires that surgical fees be paid before the procedure; this further complicates his financial struggle, as he continues to accumulate additional fees during his unnecessarily long hospital stay. This also complicates his health condition as his disease continues to progress. Throughout his stay in the hospital, the patient is being nursed daily; his wounds are being cleaned and dressed once a day. His list of medications includes oral penicillin and diclofenac.

**Discussion**

Neural tube defects (NTDs) are the second most common congenital anomalies worldwide (following congenital cardiac abnormalities) and are a common cause for chronic disabilities. Myelomeningocele is the most common form of NTD with an incidence ranging from one to seven per 1,000 live births, depending on ethnic, geographic, and nutritional factors. Myelomeningocele is the most severe birth defect that is compatible with survival. Maternal screening programmes, along with folic acid supplementation, have a significant role in the assessment and prevention on NTDs.

In some developing countries, resources for prenatal screening programmes and patients’ education levels are not sufficient to prevent and properly manage congenital NTDs; this ultimately leads to unfavourable health outcomes.

A recent study showed that myelomeningocele had the highest disease burden out of all the congenital anomalies in children born in Kenya. This burden is two-fold: there are deficits that occur as a result of the defect (paralysis, incontinence, etc.); and, a spectrum of additional sequelae, which may seem unrelated but are actually consequences of these deficits. In the case of our patient, the presentation of SCC is the end result of chronic inflammation, which indirectly resulted from the congenital defect.

**Conclusion**

Improved healthcare awareness has helped children born with NTDs to survive into adulthood in Africa. This has resulted in an emerging at-risk population for Marjolin’s ulcers, cancers that are at present rare but virulent.

Chronic non-healing ulcers, especially in this population, should carry a high index of suspicion and should be biopsied and treated urgently. Delay in diagnosis may result in poorer prognosis; early detection and close follow-up of Marjolin’s ulcers improves health outcomes significantly. In addition to direct action against Marjolin’s ulcers, aggressive public campaigns should encourage periconceptional folate supplementation and prenatal screening to help reduce the disease burden of NTDs, especially in resource-limited regions. Life-long follow-up and health education should be provided to patients with NTDs and their caregivers, focusing on pressure ulcer prevention by using proper mobility, and early treatment of ulcers. These measures will help to reduce the incidence of Marjolin’s ulcers in this high-risk population and hence reduce mortality.

**NTDs include:**
- anencephaly;
- encephalocele;
- spina bifida occulta;
- meningcele; and,
- myelomeningocele.

**Myelomeningocele might be associated with:**
- paraplegia;
- hip dislocation and talipes;
- sensory loss;
- neuropathic bladder and bowel;
- scoliosis; and,
- hydrocephalus.

**References**

Gliosarcoma: a rare variant of glioblastoma multiforme

Abstract
Gliosarcoma (GS) is a rare malignant neoplasm of the central nervous system. It is a variant of glioblastoma multiforme (GBM) consisting of both glial and sarcomatous components. This is a case of a 51-year-old, right-handed male with a history of recurrent GS, despite multiple resections, radiation therapy, and multiple rounds of chemotherapy. The patient first presented with sudden loss of comprehension, hallucinations, and aphasia. Magnetic resonance imaging (MRI) showed a left posterior parietal lobe lesion. He underwent a craniotomy with resection, postoperative radiation and chemotherapy. GBM has a high rate of recurrence, and in the two years following diagnosis, the tumour increased in size on six occasions. Over this time period, the patient underwent multiple rounds of surgery, chemotherapy, and radiation treatments. The patient survived for approximately three years after his first presentation.

Currently, the treatment of newly diagnosed GBM patients includes temozolomide chemotherapy in combination with radiation therapy. Ongoing clinical trials have also shown bevacizumab to be a useful agent in patients with recurrent GBM. The prognosis following a diagnosis of GBM has recently improved due to the introduction of drugs such as temozolomide and bevacizumab. However, the outlook is still poor. Mean survival for GBM patients with standard-of-care surgery, radiation therapy, and chemotherapy is 15 months. The rate of recurrence is high, and the treatment required is aggressive.

Introduction
Gliosarcoma (GS) is considered an exceptionally rare neoplasm, representing 1-8% of all malignant gliomas. The 2007 World Health Organisation (WHO) report on the classification of central nervous system tumours described GS as a grade four neoplasm and a variant of glioblastoma multiforme (GBM), which consists of both glial and sarcomatous components. GS has similar natural history and presentation to GBM, with a slightly higher propensity for temporal lobe involvement. GBM itself is considered the most common and aggressive form of primary malignant brain cancer.¹,²

Mean survival for patients with GBM is 15 months with standard-of-care surgery, radiotherapy and chemotherapy.³ Even with aggressive management, there is a high rate of recurrence. Patient and treatment factors associated with outcome in the GS variant are ill defined because of the small number of patients reported in the literature. One study, however, used the Surveillance, Epidemiology, and End Results (SEER) database to analyse more than 300 adult patients with GS. The most important factors influencing overall survival were identified as: age; extent of resection; and, use of adjuvant radiation therapy.³ One promising chemotherapy agent is temozolomide, an alkylating agent that methylates DNA causing apoptotic death of tumour cells, which was approved by the US Food and Drug Administration (FDA) in 2005. It has been shown to increase overall survival (OS). In one study, the combined use of temozolomide and radiation therapy showed 24-month OS of 24.2% in treated patients between 2006 and 2008, compared with 12.1% between 2000 and 2003. This may be correlated with the widespread use of temozolomide and adjuvant radiation therapy after 2005.⁴ Ongoing clinical trials have also demonstrated the benefit of anti-angiogenesis therapy in patients with recurrent GBM in the form of bevacizumab (a humanised monoclonal antibody), which binds vascular endothelial growth factor (VEGF) and inhibits formation of tumour blood vessels.⁵
Case report

We report a case of a 51-year-old, right-handed male with a history of recurrent GS post multiple resections, radiation therapy, and multiple rounds of chemotherapy. The patient first presented in November 2006 with sudden loss of comprehension, hallucinations, and aphasia. Magnetic resonance imaging (MRI) showed a left posterior parietal lobe lesion. The following month he underwent a craniotomy with gross total resection. Biopsy of the lesion at this time revealed GBM. Postoperative radiation and temozolomide adjuvant chemotherapy were administered, and a follow-up MRI showed that the tumour had regressed.

A year later, in November 2007, a repeat MRI showed tumour recurrence; a repeat craniotomy with tumour resection was performed. For a brief time the patient was able to return to work and resumed playing golf. In October 2008, he once again returned presenting with worsening symptoms of delayed word finding, expressive aphasia, and decrease in fine motor co-ordination in the right hand. An MRI (Figure 1) revealed a 4cm enhancing mass in the left temporo-parietal area suggestive of recurrent disease. The heterogeneous mass signal intensity identified was consistent with the central necrosis with cell debris found in high-grade gliomas. There was no mass effect visible on the left lateral ventricle, but it did appear to be secondarily enlarged due to local volume loss after previous resections. Basal cisterns were open and there was no evidence of hydrocephalus.

MR spectroscopy showed elevated lactate and choline associated with inflammation and necrosis, also consistent with tumour recurrence. A functional MRI (fMRI) scan revealed that the recurrent tumour was very close to Wernicke’s area. A left temporo-parietal craniotomy with tumour resection and biopsy was performed with awake, intra-operative language mapping, motor evoked potential, and somatosensory evoked potential monitoring to avoid iatrogenic functional loss. Post-operatively, the patient was started on irinotecan chemotherapy and bevacizumab. Tissue biopsy was sent for haematoxylin and eosin (H&E) staining to mark for features of malignancy, and immunohistochemistry (IHC) staining to mark for glial and sarcomatous components. Sarcomatous components were present; nuclear pleomorphism and increased mitotic activity were noted (Figure 2). H&E staining also showed vascular proliferation with myxoid and chondromatous areas (Figure 3). IHC staining showed positive glial fibrillary acidic protein (GFAP) antibody staining for the glial component and positive reticulin staining for the sarcomatous component.

Beginning approximately three years after diagnosis, the tumour began to grow more aggressively and the chemotherapy regime was changed accordingly. The patient was initially on carboplatin and bevacizumab for one month; however, the tumour continued to grow and the patient was then put on etoposide and bevacizumab. When this failed to halt tumour progression, the chemotherapy regimen was changed to procarbazine accompanied by bevacizumab. During his last visit, the patient presented with nephrotic syndrome, likely secondary to bevacizumab. His neurological exam at this stage showed impaired comprehension; the patient was able to follow one-step but not two-step commands, most likely as a result of the lesion in Wernicke’s area. He also had a right homonymous hemianopia and decreased pinprick sensation on the right side of his face, consistent with previous post-contrast coronal MRIs that showed abnormal leptomeningeal enhancement involving the optic nerves, anterior chiasm, and seventh and eight cranial nerves within the internal auditory canal.

Because the patient became thrombocytopenic, procarbazine was discontinued. He was treated with dexamethasone, an oral corticosteroid, for his thrombocytopenia and bowel incontinence. Dexamethasone also prevents brain oedema and raised intracranial pressure, and could potentially help to alleviate the patient’s confusion. The patient was discharged home with a prescription for a hospital bed and received palliative care. Unfortunately, the patient survived only 35 months from first presentation.

Mean survival in gliosarcoma is 15 months with standard-of-care treatment. Variations of prognosis in individuals may be due to individual clinicians and their management, namely the extent of resected margins and whether gross total resection is possible. With regard to the poor prognosis associated with GBM, clinical trials are ongoing in search of the optimal treatment. Current treatment strategies include temozolomide for newly diagnosed GBM, and bevacizumab in combination with temozolomide for recurrent GBM.
Discussion

The low incidence of GS means that there are a small number of cases, which has made it difficult to characterise the disease. However, the epidemiology, clinical and radiological features, and neurological sequelae of GS are very similar to those of GBM and thus treatment is usually the same. While the first line of treatment for newly diagnosed GBM patients is radiation therapy in combination with temozolomide, there is still no standard of care for recurrent GBM. GBM has a high rate of recurrence, and response to treatment is seen in less than 10% of patients. This may prove to be an area of importance when exploring strategies to improve prognosis. In 2005, a phase III randomised clinical trial showed that postoperative radiation and concurrent temozolomide, followed by maintenance temozolomide for six months, improved median survival in newly diagnosed GBM patients from 12.1 months to 14.6 months, as compared with radiation therapy alone. This regimen is now the standard of care for newly diagnosed GBM. There is currently no prospective evidence to justify the use of temozolomide in GS patients specifically; however, a small retrospective series showed similar clinical outcomes in patients with GS compared to GBM. The current guidelines set by the National Comprehensive Cancer Network (NCCN) recommend that patients with GS undergo the same treatment as patients with GBM following maximal safe surgical resection. In 2009, the FDA approved bevacizumab, a promising treatment approach that targets the tumour’s blood supply. GBMs are highly vascularised tumours and express high levels of vascular endothelial growth factor (VEGF). Bevacizumab, a humanised monoclonal antibody that targets VEGF, has shown promise as an angiogenic inhibitor. When used in combination with temozolomide chemotherapy, bevacizumab has shown positive results in two prospective phase two studies and was granted accelerated approval by the FDA as a therapeutic agent for recurrent GBM. A recent retrospective study demonstrated that bevacizumab was more effective in older patients (≥55 years); the authors hypothesised that this may be due to differences in levels of VEGF expression in different age groups. Patients who relapse after initial response to bevacizumab are a particularly challenging group to treat, since there is no consensus on their optimal treatment. Current strategies include: discontinuing bevacizumab and treating with either alternative cytotoxic chemotherapy or an investigational agent; or, more commonly, continuing with bevacizumab and adding another chemotherapy agent such as carboplatin.

Conclusion

Ongoing clinical trials have shown the benefit of anti-angiogenesis therapy in the treatment of recurrent GBM. However, there are still unknown aspects of the use of bevacizumab, such as optimal dosage and treatment duration, which chemotherapeutic partner should be used, and what the best criteria are for measuring radiographic response. Ongoing clinical trials will be key in addressing these issues. Outcomes may depend on factors such as individual clinicians and their management, in particular whether gross total resection of the tumour is performed. Finally, differences in survival may be correlated with patient factors, namely response to treatment. The patient presented surpassed the mean survival while being treated with bevacizumab among other agents. Further studies may help us to understand why certain cohorts of patients respond more favourably than others. Until then, GBM, including GS, remains particularly challenging to treat due to the high rate of recurrence. The key to improving survival may lie in studies exploring individual clinician’s management, patient response to treatment, and the optimal use of bevacizumab.

References

MRSA of unknown aetiology causing prostate abscess in a patient with incidental prostate adenocarcinoma

Abstract
Community-acquired methicillin resistant Staphylococcus aureus (CA-MRSA) infection is a relatively under-recognised cause of bacterial prostatitis. This report presents a case of bacterial prostatitis due to CA-MRSA in a patient with an additional incidental finding of prostate adenocarcinoma. Our patient presented with urinary symptoms and worsening suprapubic pain. A magnetic resonance imaging (MRI) scan revealed an abscess in the prostate, which was drained. A decision was made to treat him with antibiotics delivered via a peripherally inserted central catheter (PICC) line for six weeks. Unfortunately, due to lack of insurance, he was unable to complete treatment. An incidental prostatic mass was biopsied and identified as adenocarcinoma with unusual cytology. Though studies have not confirmed a correlation between chronic inflammation and prostate adenocarcinoma, the relationship between persistent inflammatory states and neoplasia is known in other cancers. The unusual presentation of this patient may suggest that CA-MRSA prostatitis may have contributed to the development of a prostatic adenoma.

Introduction
Acute bacterial prostatitis is relatively common in patients with risk factors such as diabetes mellitus, cirrhosis and suppressed immune system. The bacteria can be introduced via an ascending infection, or through iatrogenic procedures such as prostate biopsy. The most common causative organisms are Escherichia coli and Enterococcus. The incidence of community-acquired methicillin resistant Staphylococcus aureus (CA-MRSA) infection as a cause of prostate abscess is quite low. There are only nine published case reports in PubMed where a prostate abscess is noted to be caused by CA-MRSA. In this article we discuss a case of bacterial prostatitis with CA-MRSA abscess in a patient with no significant risk factors, who was also incidentally found to have prostate adenocarcinoma.

Case report
This is a case of a 44-year-old African-American gentleman, Mr WS, who presented to the Emergency Department (ED) on July 13, 2013, complaining of a one-day history of localised suprapubic abdominal pain, dysuria and urinary retention. He also had a history of back pain around the lower lumbar region, which had worsened over the last three days, and during which he also reported subjective fever and chills. He denied any night sweats. He reported neither haematuria nor difficulties with passing stool. At presentation, his suprapubic pain was a 7 out of 10. He denied urgency, frequency or incomplete voiding. His past medical history did not reveal any history of urinary retention or any other genitourinary symptoms. Mr WS’s past medical history was significant for a gunshot wound on his left lower leg in 2000, and a neck abscess, which was incised and drained in 1996. He did not take any medications at home. His family history was non-contributory. He had a 25-pack year history of smoking, but did not drink alcohol. He also admitted to engaging in illegal substance use (such as cocaine) but did not disclose his method of intake. On examination, Mr WS was alert and oriented. His vitals were: temperature 98ºF, blood pressure 155/89mmHg, respiratory rate 16, and O₂ saturation of 99% on room air. On palpation, his abdomen was tender and full around the suprapubic region. There was perianal anaesthesia; however, a digital rectal examination (DRE) was refused. There was mild lumbosacral tenderness bilaterally but no step off and no costovertebral angle tenderness. His cardiovascular, respiratory and neurological exams were non-contributory. In the ED, the patient was given a litre of IV fluids and a Foley catheter was inserted, which drained more than a litre of fluid. He was given another litre of IV fluids, but only managed to excrete 10-20mL on his own. His bladder scan revealed more than 250cc of fluid; a Foley catheter was reinserted. His urine cultures were negative for Chlamydia trachomatis, Neisseria gonorrhoea and Trichomonas vaginalis. His urinalysis revealed yellow hazy urine with red blood cells of 6-10 units per high power field (HPF), white blood cells of 0-2 units per HPF and presence of mucus.

Tisa Saha
RCSI medical student
Urinalysis was negative for glucose and protein level was 25mg/dL. He had a non-contrast magnetic resonance imaging (MRI) that revealed small herniated discs at L2-3, L3-4, L4-5 and L5-S1, with no visible acute changes or compression of the cauda equina. No epidural abscess collections were noted. He was discharged home with a Foley catheter in situ and told to follow up with his urologist in two days or return to the ED if he could not follow up due to lack of insurance. Two days post discharge, Mr WS returned to the ED requesting the removal of his catheter. He was in severe pain, which he rated 10 out of 10, and reported haematuria. His vitals were: blood pressure of 112/77mmHg, temperature 98.2°C, respiratory rate 16, and O2 saturation of 99% on room air. His urinalysis was significant for red blood cell count of 3-5 per HPF, white blood cell count of 11-20 per HPF, grossly positive for blood, leukocyte esterase level of 500/uL and protein level of 25mg/dL. He was given a litre of IV fluid, paracetamol and IV ceftriaxone. He soon became afebrile and was able to urinate on his own. His bladder scan revealed 54ml of fluid after voiding 100ml of urine. He was discharged soon after on oral medications due to lack of insurance and speed recovery from prostate abscess. However, the challenge is identifying the disease itself, which requires a high index of suspicion. In our case, the diagnosis was not confirmed until a contrast CT of the abdomen was performed on the third admission and blood cultures came back positive.

Discussion

Among the few published cases of MRSA prostatitis, most of the patients have some associated comorbidity or risk factor such as IV drug abuse (IVDA) or diabetes mellitus. It is highly likely that with a past medical history of a neck abscess, our patient could have been engaging in IV drug abuse due to the lack of insurance, follow-up from this patient is highly unlikely. However, this case is also unique due to the incidental finding of a prostate cancer. It has been noted in prior case reports that prompt treatment with IV antibiotics such as IV vancomycin, trimethoprim-sulfamethoxazole and rifampin, as well as transurethral resection of prostate, can reduce hospital admission days and speed recovery from prostate abscess. However, the challenge is identifying the disease itself, which requires a high index of suspicion.

References

2. Naboush A, Abou Yassine A, Yasmin M, Mobarakai N. Community-acquired methicillin-resistant Staphylococcus aureus (MRSA). One out of the four vials of blood taken for culture on his initial admission and four out of four taken on his second admission returned positive for MRSA. Mr WS was called to return to the ED for further evaluation. He denied any skin infections, abscesses, history of IV drug use, cough or shortness of breath. He still had significant dysuria and reported new increased frequency. He denied any haematuria. His last cocaine use was six days previously. New findings on his examination included bilateral inguinal lymphadenopathy and suprapubic tenderness of increased severity. His inguinal region and penile shaft appeared normal. His DRE was not completed due to severe pain; however, a severely tender and enlarged prostate was evident.

The rest of the examination was non-contributory. His vitals were stable and he was afebrile. His toxicology reports were negative. He was started on IV vancomycin 1.25g every 12 hours. Other tests performed included a transoesophageal echocardiography and a chest x-ray, which did not reveal any significant findings. Due to severe pain, an ultrasound of the prostate was not performed and instead a computed tomography (CT) with contrast was performed, which revealed multiloculated fluid collection with peripheral enhancement that measured approximately 5x6.4x5.1cm. The mural lining was thickened in the anterior superior portion of the distended bladder, suggestive of adenocarcinoma. No epidural abscess collections were noted. He was discharged home with a Foley catheter. He was scheduled to return to the clinic for further follow-up or if there was deterioration in his health.
Omalizumab in the treatment of severe persistent IgE-mediated asthma

Abstract
Over 300 million people worldwide suffer from asthma, a chronic respiratory condition characterised by airway obstruction, inflammation and bronchial hyperresponsiveness. This figure is set to rise to 400 million by 2025. Despite a wide variety of treatment protocols and guidelines available for alleviation of symptoms, 5-10% of patients with asthma are non-responsive and are said to have severe, persistent (or refractory) asthma. These patients account for the majority of disease burden on the healthcare system in terms of mortality, morbidity and treatment costs. In approximately 50-80% of these patients, asthma is mediated by immunoglobulin E (IgE), which is critical in the inflammatory cascade. Omalizumab is a humanised monoclonal anti-IgE antibody used in the treatment of severe allergic asthma. It works by inhibiting cellular IgE binding and reducing the number of IgE receptors on pro-inflammatory cells. It has been shown to improve symptoms and quality of life, and reduce asthma exacerbations and the need for systemic corticosteroids. This review will look at the socioeconomic impact of severe allergic asthma on the Irish population and give a cost–benefit analysis of omalizumab and guidelines for its use in patients. Furthermore, it will discuss how to best optimise its use in the management of people with severe asthma, and illustrate the importance of critically reviewing trial data that is used to formulate and re-appraise guidelines in clinical practice.
Introduction

Asthma is a chronic respiratory disease of heterogenous aetiology with varied pathological and clinical phenotypes. It is characterised by differing patterns of airway inflammation associated with a plethora of pro-inflammatory cell types, which lead to bronchial hyperresponsiveness and airway obstruction. Over 300 million people globally are affected by asthma, a figure that epidemiologists expect will continue to increase. This is due to a complex and incompletely elucidated interaction between a genetic predisposition to atopy and environmental factors. Certain stimuli trigger a pathologically exacerbated bronchoconstriction in affected patients; these include certain weather conditions (cold, damp climate), perennial aeroallergens (e.g., dust mites, airborne pollutants), and respiratory viruses. Exposure to these allergens leads to a pro-inflammatory cascade, which can persistently cause debilitating and even fatal symptoms such as dyspnoea, wheezing, chest tightness and coughing. The majority of patients manage their symptoms with a combination of environmental control and pharmacological agents, which include β2-adrenergic receptor agonists and corticosteroids as per the Global Initiative for the Management of Asthma (GINA) guidelines. The small percentage of patients with asthma (5-10%) who, despite this treatment, still have recurrent symptoms, are said to have severe or refractory asthma. The inadequate control of symptoms, in conjunction with confounding comorbidities such as rhinitis, sinusitis and obstructive sleep apnoea, results in a poor quality of life. These patients account for the most significant burden on healthcare services, as they frequently access emergency services and often require long-term hospital admissions and expensive chronic therapeutic intervention. There are also heavy socioeconomic costs related to loss of work or school days in this group. The classification of “severe persistent” or “refractory” asthma proposed by the American Thoracic Society (ATS) requires that patients are compliant with medication, that other conditions are excluded, and that other environmental factors are treated. It also requires the patient to be on glucocorticoid treatment, fulfilling one of the following two major criteria for maintenance of control:

- continuous or near continuous (≥50% of the year) treatment with oral glucocorticoids; or,
- treatment with high-dose inhaled glucocorticoids.

Furthermore, the patient is required to fulfill two of the following seven minor criteria:

- short-acting β-agonist for near-daily control of asthma symptoms;
- daily treatment with ‘controller’ medication (e.g., long acting β-agonist, theophylline or leukotriene antagonist);
- persistent airflow limitation (with a forced expiratory volume in the first second or FEV₁ <80% predicted with >20% diurnal variability in peak expiratory flow);
- at least one urgent care visit for asthma per year;
- three or more oral steroid ‘bursts’ needed for treatment per year;
- rapid deterioration with ≤25% reduction in oral or inhaled glucocorticoid dose; or,
- at least one near-fatal asthmatic event in the past.

The European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA), a multi-centred, cross-sectional study, was the first comprehensive assessment of severe asthma in Europe. The data gathered by ENFUMOSA suggested that severe asthma was a distinct clinical entity compared to mild to moderate asthma, with structural changes in airway remodelling being a key feature of severe asthma. According to the Asthma Insights and Realities in Ireland (AIRI) study in 2005, there were approximately 470,000 asthma sufferers in Ireland, the fourth highest prevalence globally. It is estimated that one in ten adults and one in five children under the age of 14 in Ireland suffer from asthma. Furthermore, 90,000 people are said to have inadequate symptom control and Irish adults with asthma lose on average 12 days from work yearly, while children lose ten school days yearly. The Asthma Society of Ireland estimates that 6,300 Irish people with asthma meet the criteria for severe asthma, with up to 100 deaths annually in Ireland. The total cost to Ireland in 2003 due to asthma was reported to be €463 million, with €227 million accounting for emergency care and hospitalisation.

Omalizumab

Omalizumab (Xolair) is a recombinant humanised monoclonal anti-IgE antibody that is used in the treatment of severe atopic asthma. IgE is a critical mediator in allergic diseases such as asthma. Following exposure to a stimulant, allergic individuals produce allergen-specific IgE. Circulating IgE attaches to pro-inflammatory cells such as mast cells, basophils and macrophages via the Fc portion linked to Fc-epsilon-RI receptors. Upon further allergen exposure, cross-bridging of IgE and allergen on the surface of effector cells leads to the release of inflammatory mediators such as histamine, prostaglandins and leukotrienes.

In people with asthma, chronically high serum IgE levels potentiate this system, leading to airway inflammation and bronchial hyperresponsiveness. It is estimated that 50-80% of treatment-resistant patients have an allergic component, with IgE playing a key role in the triggering and maintenance of airway inflammation and an exaggerated bronchoconstrictive response. Anti-IgE therapy was included in 2006 within step 5 of the GINA guidelines as an add-on to corticosteroids, long-acting β2-agonists and/or other controller medications. Omalizumab works by binding free serum IgE at Fc-epsilon-RI, the site that normally binds receptors on mast cells and basophils. This prevents cross-linking of receptors and subsequent degranulation and release of pro-inflammatory mediators. Perhaps as a result of decreased circulating free IgE, the drug
Omalizumab is illustrated in mast cells and basophils over time. The mechanism of action for causes a decrease in the number of cell-surface IgE receptors of mast cells and basophils over time. The mechanism of action for omalizumab is illustrated in Figure 1. In 2005, the European Medicines Agency (EMA) issued a marketing licence for the use of omalizumab as an add-on therapy for patients with severe persistent allergic asthma aged 12 and above; this license was extended in 2009 to include children over the age of six. In 2006, a Cochrane review of 14 trials looked at the response of 3,143 patients with mild to severe IgE-mediated asthma and found omalizumab to be generally well tolerated, with positive physician and patient assessments. There was a clinically significant number of patients who were able to reduce or withdraw their inhaled corticosteroid (ICS) use compared to placebo. There was also a reduction in the frequency of asthma exacerbations when omalizumab was used as an add-on with ICS. However, “impressive” placebo effects were noted in the control groups, bringing into question the “true” effects of omalizumab and suggesting that the clinical value of steroid reduction has to be weighed against the costs of the drug. Cost–benefit analysis of omalizumab The dosage of omalizumab is dependent on the patient’s body weight and the total serum baseline IgE level. It is currently approved in the European Union for patients with allergic asthma with total plasma IgE levels ranging from 30-1500IU/mL with a dosing formula of 0.016mg/kg per IU/mL. Following subcutaneous administration, omalizumab has a bioavailability of 62% and induces a reversible reduction of unbound serum IgE by at least 84%, which can last up to six weeks. Currently, a physician’s evaluation is recommended 16 weeks after commencing therapy. The cost of omalizumab is £256.16 for a 150mg vial and £128.07 for a 75mg vial. The drug is administered every two to four weeks, with a fortnightly maximal dosage of 600mg. The cost per patient can be up to £26,640 per annum, with the average yearly cost for adults and adolescents being £8,056, and £8,455 for children aged six to 11. In contrast, the standard treatment regimen for those with severe asthma consists of inhaled high-dose corticosteroids, long-acting beta agonists (LABAs), leukotriene receptor antagonists, theophyllines and oral corticosteroids, along with smoking cessation (if clinically appropriate). The costs per annum for standard therapy are estimated to be £1,197 for adults and adolescents, and £810 for children. A multi-centred, observational, retrospective cohort study of 63 Irish patients was conducted, which compared clinical outcomes six months before and after treatment with omalizumab. Their findings (all p<0.0001) showed:
- a 61% decrease in asthma exacerbations;
- a 67% decrease in hospital admissions;
- a 68% decrease in bed days (a saving of 12 bed days per patient);
- a 62% decrease in courses of oral corticosteroids required; and,
- a 90% decrease in work days lost.

Cost saving for the patients who responded to omalizumab was £834 per patient over six months, mainly due to a drastic reduction in hospital admissions and bed stays.

Current guidelines
The United Kingdom’s National Institute for Health and Clinical Excellence (NICE) recommended the use of omalizumab first in 2007 for patients aged 12 years or above as an add-on treatment for severe, persistent allergic asthma. NICE also specified that omalizumab should be limited to patients who, within the past year, had more than two hospital admissions, or one admission plus two emergency department admissions, for asthma exacerbations. The evidence reviewed in their appraisal found that the number needed to treat (NNT) in one year to prevent one clinically significant asthma exacerbation (defined as peak flow or FEV1 <60% of personal best) was 2.2. In 2010, despite the EMA’s recommendation of the treatment for children six to 11 years old one year earlier, NICE stated that the cost per quality adjusted life year (QALY) gained for that age group was higher than what NICE considered cost-effective. Furthermore, a study of 510 UK patients with severe asthma found that only 27 (or 5.3%) were eligible for treatment, with NICE’s prescribing guidelines requiring hospital admissions for patients within the past year. In response to NICE’s re-appraisal in 2010, some of the UK’s leading paediatric pulmonologists contested the way the QALYs were calculated, saying they lacked an appreciation of the importance of asthmatic exacerbations and disrupted schooling when measuring paediatric QALY. In the same editorial, NICE was also criticised for having only one paediatrician on the 34-member committee that formulated the new guidelines. In November 2012, NICE’s assessment panel withdrew their recommendation of omalizumab as a cost-effective therapy altogether for both adolescents and adults, citing a lack of quantifiable data to justify omalizumab as a cost-effective use of NHS resources. However, in March 2013, NICE reversed its position and expanded the recommendation to include adults, adolescents and children aged six and over. The requirement for hospital admissions was also removed. The panel acknowledged the conclusions of clinical experts...
who pointed out that in clinical practice, patients receiving omalizumab had much more severe asthma than those enrolled in studies, and trial evidence therefore underestimated the benefits gained. Novartis also agreed to make omalizumab available to the NHS under a patient access scheme at a discounted price. This lowered the cost-effectiveness ratio to £23,200 per QALY gained, which was within the range of £20,000–£30,000 – the range that NICE considers cost-effective. The guidelines will be reviewed again in March 2016.

**Future perspectives**

The latest decision by NICE was welcomed by asthma charities and groups in the United Kingdom and in Ireland. In 2011, Novartis Ireland said they would introduce the Xolair Patient Outcomes Reimbursement Programme – a programme that would refund stock used by patients who were not benefitting at the 16-week evaluation point that is used to evaluate efficacy and to determine whether to continue with treatment. The Asthma Society of Ireland has stated, however, that omalizumab is not reimbursable under any Government schemes, and access depends on hospitals’ pharmacy budgets; this means that the drug is unavailable to 50% of patients who need it.

While omalizumab is a significant advancement as an add-on treatment for severe persistent atopic asthma, it is imperative that it is targeted at those most likely to benefit. This can be achieved by ensuring that only patients who are genuinely treatment resistant are referred to specialists for consideration of anti-IgE therapy. Isolation of these patients may be facilitated by better education with regard to medication (e.g., correct use of inhalers) and environmental control. Nurse-led home visits to 71 children in the UK diagnosed with severe asthma showed that more than half had potentially reversible factors, including inadequate adherence to medication, along with tobacco and allergen exposure at home. Furthermore, the 16-week guideline for assessing its efficacy may be flawed, as it presupposes that omalizumab is responsible for the improvement in clinical parameters as opposed to other factors. There are also doubts as to whether IgE levels are directly correlated with efficacy of therapy. Studies of omalizumab’s effect on pulmonary function tests such as FEV1 have shown inconsistent results. However, in certain patients, omalizumab decreases biomarkers of T2 inflammation such as fractional exhaled nitric oxide, peripheral blood eosinophil count, serum periostin and endothelin-1 in exhaled breath condensate. This has been shown to correlate with improved spirometry parameters and reductions in protocol-defined asthma exacerbations. The feasibility of their use as prognostic indicators of omalizumab efficacy in treatment for asthma and accurately identifying responders may be worth exploring in clinical practice. For many patients, asthma remains a severely debilitating condition. Omalizumab has provided a better quality of life for patients with severe asthma for whom treatment options are otherwise limited. However, it is imperative, given the costs associated with the drug, that it is used judiciously and targeted at those most likely to benefit.

Furthermore, there needs to be a scrupulous methodology used when calculating QALY, which takes into account various socioeconomic factors along with the input of clinicians, epidemiologists and patient groups.

**References**


27. Burton AJ, Hargadon B, Murphy AC et al. P2O The eligibility of patients with difficult asthma for omalizumab since the change to the treatment criteria. Thorax. 2010;65:84-5.
Serotonin – the missing link between myocardial infarction and suicide

Abstract
The prevalence of myocardial infarction (MI) and suicide has risen over the past 40 years in Ireland, causing considerable societal burdens. Interestingly, these conditions share common underlying pathologies, including abnormalities in both serotonin levels and platelet cell signalling function. Serotonin levels are decreased in the brains of depressed patients and in the cerebral spinal fluid of suicidal patients. A single serotonin transporter (SERT) regulates the release of serotonin stored within platelets and promotes platelet aggregation. Limitations of antiplatelet therapies necessitate novel therapeutic approaches for treating patients who have suffered an MI. The hypothesised underlying biochemical abnormality shared by suicide and MI suggests a role for the use of antidepressants in treating and preventing both of these diseases.

Introduction – two problems worth solving
Suicide rates have risen exponentially in Ireland since the 1970s and are currently regarded as being at an epidemic level. The rates for males are particularly alarming, having doubled from 18.3 per 100,000 in 1989 to 39.9 per 100,000 of the population. Similarly, mortality rates in Ireland from ischaemic heart disease rose steadily until they plateaued at an alarmingly high rate in the 1970s and onward. Between 1970 and 1999, 46-53% of deaths in Ireland were attributed to ischaemic heart disease. Currently, ischaemic heart disease and suicide are the first and ninth leading causes of death in Ireland, respectively. These overwhelming societal burdens appear to be rising in conjunction with one another and exploration is required to determine if they are arising from a common aetiology, and thus may be treated by targeting the same biochemical process.

Epidemiology – myocardial infarction and suicide
In a 2013 Danish study, Larsen et al. explored depression following MI and found that depression itself was an independent risk factor...
for recurrent MIs. All patients over the age of 18 who were discharged following an MI (ICD-10 code I21) in 2009 in the Central Denmark Region were invited to participate. One in five (of the 589 who enrolled) was diagnosed with depression in the three months post MI. Furthermore, MIs were associated with a 1.53 times higher risk of suicide than in the general population. Fortunately, moderate to severe depressive symptoms in post-MI patients may be successfully reduced through the use of antidepressants (effect size, 0.66; 95% CI, 0.38-0.94). Selective serotonin reuptake inhibitors (SSRIs) are used preferentially over tricyclic antidepressants in this population because of the adverse cardiovascular events, such as prolonged QT interval, associated with tricyclic antidepressants. The study by Larsen et al. illustrates the close association between ischaemic heart disease and depression. It also highlights adverse prognostic outcomes post MI imparted by comorbid depression, including new cardiovascular events or death, in addition to patients’ increased predisposition to suicide.

**Exploration of biochemical imbalances**

In an attempt to identify the biological markers for suicidality, Pandey et al. obtained platelets, lymphocytes, and cerebrospinal fluid from the peripheral tissue of suicidal patients or from brains of suicide victims obtained post mortem. They reported variations in cytokine levels and lymphocyte gene expression in depressed patients. The maximum number of binding sites of serotonin receptors on platelets was significantly higher in suicidal patients, to an effect size of 1.12 when compared to normal control subjects. Abnormalities of serotonin levels (such as decreased CSF 5-HIAA) and in platelet signalling (such as increased SHT2A receptors in platelets) point to physiological changes that may aid in the identification of patients predisposed to suicidal behaviours, as well as the elucidation of novel targets for treatments aimed at suicide prevention. Current biological therapy for depression is based upon correcting the hypothesised underlying biochemical abnormality of decreased serotonin levels in the brain. Likewise, SSRIs may be efficacious when added to a biopsychosocial regimen for patients without a clear history of depression, but who are at risk of suicide. Given the finding of abnormal plasma serotonin in suicidal patients, the rationale for the use of these drugs for suicide prevention is similar to that for its use in depression. This observed relationship has been confirmed by studies such as that conducted by Ruljancic et al., which demonstrated a positive correlation between serotonin concentrations and healthy controls as compared to a negative correlation between serotonin levels in suicidal and non-suicidal depressed patients.

Serotonin dysregulation also has a role in the pathophysiology of coronary artery disease. Increased plasma levels of serotonin were seen by Breeener et al. in serum samples of patients with hypertension. Normally, a serotonin transporter (SERT) regulates plasma levels by transporting free serotonin into platelets to be stored; this occurs through a negative feedback mechanism. By regulating serotonin plasma levels, SERT counters the pathological vasoconstriction that contributes to hypertension. Serotonin contributes to systemic vascular vasodilation by relaxing smooth muscle, inhibiting sympathetic tone, and increasing endothelium-derived relaxing factor. SERT also plays a part in promoting platelet aggregation, a key pathophysiologic process contributing to ischaemic heart disease. Patients expressing high levels of SERT – thus having low levels of serotonin in the circulation – are not only likely to have hypertension as a result, but are also at even greater risk of MI because of a greater propensity for platelet aggregation.

In light of these biochemical mechanisms, SERT is a promising biochemical marker; it has the potential to explain a common underlying pathophysiologic abnormality that predisposes to both suicide and coronary artery disease.

**Novel therapeutic approaches for post-MI therapy**

Currently, antiplatelet drugs are a central component of post-MI therapy. Aspirin and dipyridamole inhibit platelet aggregation through thromboxane synthesis inhibition at the level of cyclooxygenase and thromboxane synthase, respectively. Compliant patients respond positively to aspirin therapy; however, patients do not respond in the same manner to other antiplatelet drugs such as clopidogrel. In an abstract from the 2012 International Congress on Thrombosis, Cattaneo et al. stated that one-third of patients are poor responders to clopidogrel, highlighting the highly variable pharmacological response to antiplatelet agents. These findings demonstrate a role for personalised medicine in the treatment of patients at risk for or following MI, and suggest the possibility of varying underlying processes contributing to thrombus formation causing cardiovascular disease. The inverse relationship between plasma serotonin levels and MI, along with the demonstrated comorbidities of depression and suicidal ideation, suggest that SERT and serotonin may be interesting new targets for potential exploitation in the post-MI medical discharge plan. Serotonin and the catecholamines (dopamine, epinephrine and norepinephrine) are all monoamine neurotransmitters whose receptors have been implicated in von Willebrand factor-mediated platelet thrombus formation. By increasing plasma serotonin levels, negative feedback mechanisms mediated by SERT would decrease platelet serotonin receptors, subsequently reducing platelet thrombus formation. The use of medications that manipulate serotonin may confer the additional benefit of mitigating depression and suicidal ideation. Both are independent risk factors for recurrent MIs and have been shown to be associated with low levels of serotonin in the brain. Developing an effective protocol for the prevention and treatment of MI and suicide is feasible given the evidence of a shared biochemical target. Patient accessibility factors are a concern when attempting to prevent consequences of mental health problems. However, a study conducted in the United States found that 81% of individuals who died by suicide attended healthcare services within one year prior to their death. This suggests a potential role for active screening to detect patients at risk of suicide. Early interventions and preventive measures targeted at these high-risk...
individuals could be employed to reduce the incidence of suicide and self-harm. Such preventive measures may include interventions aimed at increasing plasma serotonin levels. Dietary supplementation with tryptophan rich egg protein hydrolysate, for example, has been shown to increase tryptophan availability for serotonin production. This effectively reduced depressed mood in all test subjects and improved their perceptual and motor responses, both of which are decreased in patients with depression.16 Additionally, those patients who suffer from, and survive MIs may benefit from treatments that increase their serotonin levels, such as SSRIs. Hypothesised benefits include reduction of platelet-induced thrombus formation as well as treatment for post-MI depression, both of which increase the risk of MI recurrence. SSRIs may also prove effective in modulating platelet function in patients who are refractory to treatment using traditional anti-platelet medications such as clopidogrel, thus contributing to an arsenal of therapeutic options to personalise medical treatment post MI.

Conclusion
Given the relationship between low brain serotonin levels and suicide, as well as the role of serotonin in thrombus formation central to the pathophysiology of MI, it appears that serotonin may be an aetiological link between these two leading causes of death in Ireland. The costs to families and society of premature death due to these conditions is enormous. Heart disease remains the leading cause of mortality in Ireland and this is further compounded by the high prevalence of depression in this patient population.2,4 The Department of Economics at the National University in Galway estimated the total cost of suicide at over €906 million in 2001 due to workforce absence and health service utilisation.13 The poor financial climate in Ireland will be further burdened by the continually increasing suicide rates, especially prevalent in young men who are so crucial to the workforce and societal function.16,17 The emotional consequences of suicide for family, friends, and society are massive, highlighting the importance of combatting this issue.

The finding of low plasma serotonin levels contributing to depression and consequently suicide, as well as platelet plug formation and resultant MI, is promising in providing an explanation for the pathophysiology behind and treatment of MI recurrence and the aggravating comorbidity depression. The targeted utilisation of SSRIs in patients post MI may prove beneficial by addressing a common underlying biochemical abnormality contributing to MI recurrence, as well as to depression and suicide.

References
Rediscovering thalidomide: lessons learnt and evolving indications

Abstract
Thalidomide (α-phthalimido-glutarimide), a hypnotic sedative and anxiolytic with anti-emetic properties, was withdrawn in 1961 after four short years on the drug market. Prescribed to pregnant women to reduce morning sickness, it was found to cause limb and other malformations in newborns. The huge scale of the catastrophe was attributed to the presumption of thalidomide’s safety, combined with relaxed drug safety regulations and irresponsible actions on the part of the drug company. Since then, thalidomide has driven a revolution both in drug safety legislation and in the way pharmaceutical compounds are researched – for example, through its demonstration of species specificity. Several potential mechanisms by which thalidomide induces teratogenesis have been proposed, of which three widely supported hypotheses will be discussed.

Thalidomide has not disappeared from clinical use, however. It was first tried in erythema nodosum leprosum (ENL) three years after its withdrawal with impressive success. Two classes of analogues – immunomodulatory drugs (IMiDs) and selective-cytokine-inhibitory drugs (SelCIDs) have been developed to enhance efficacy and reduce toxicities. Today, thalidomide and IMiDs are the approved treatments for ENL, multiple myeloma and myelodysplastic syndrome. Despite knowledge about the activities of these drugs, their exact mechanisms of action are only known for a few diseases, including multiple myeloma. Thalidomide and IMiDs are currently being studied in solid tumours, HIV-associated diseases and refractory dermatological conditions. The future of thalidomide and its derivatives in the mentioned fields are summarised in this review.

Introduction
Thalidomide was developed by the German pharmaceutical company Chemie Grünenthal as part of a search for an easier and cheaper method to synthesise antibiotics.¹ It had neither the antibiotic nor any of the other pharmacological properties being tested for in animals; however, thalidomide was believed to be a human sedative due to its structural similarity to barbiturates.¹ The low lethal dose of barbiturates gave thalidomide huge market potential as a non-toxic tranquiliser.¹ Upon finding that a lethal dose was indeterminable in rats, Grünenthal proceeded with human trials of effectiveness.¹ Following its approval in 1957, thalidomide was sold over the counter to treat ailments from colds to insomnia.¹² Though no specific studies had been done, thalidomide was claimed to be safe for pregnant women.¹ Mild to severe side effects such as dizziness, ‘hangover’, allergy and peripheral neuropathy were reported.¹ Although healthcare providers pressured the US Food and Drug Administration (FDA) to put thalidomide under prescription, no action was taken to control its usage.¹ In 1961, Lenz and McBride independently published a link between maternal consumption of thalidomide and limb malformations among neonates, mainly phocomelia (short limbs with hands and feet located much nearer to the trunk).³⁴ Other less common thalidomide-associated defects include external ear, eye, kidney, spinal cord, heart and gastrointestinal abnormalities.⁵⁶ Although thalidomide was immediately withdrawn from the market, 10,000 malformed babies had been born worldwide and an incalculable number of spontaneous abortions had occurred.⁵⁶ A single dose of thalidomide taken between 20 and 36 days after fertilisation – the period of limb development – is sufficient to cause malformations in 20-30% of newborns.⁵⁷ Today, 5,000 survivors still live with its impacts.¹ Nevertheless, new discoveries made over the last five decades have returned thalidomide to the market, albeit for different indications. This review will discuss lessons learnt from this medical tragedy, as well as the current and potential clinical applications of thalidomide.
Lessons learnt

Revolution in drug safety

The damage caused by thalidomide could have been minimised if Grünenthal had undertaken more vigorous trials and post-marketing monitoring. When doctors suspected thalidomide as the culprit for peripheral neuropathy and birth defects, Grünenthal denied all claims and repeatedly distributed letters re-affirming thalidomide’s safety without further scientific proof.¹ The generally lenient atmosphere surrounding approval of new pharmaceutical agents during the 1960s allowed potentially dangerous drugs like thalidomide to remain on the market unchecked. For example, new drugs submitted for approval in the United States were cleared automatically if the FDA was unable to disprove their safety within 60 days of application.¹ Clinical trials required no pre-approval and were subject to minimal guidelines.¹ In response to thalidomide, however, the FDA’s Dr Frances Kelsey demanded solid evidence of the drug’s safety – not a common practice 50 years ago.¹ Even so, thalidomide was distributed to 20,000 patients in the US alone.¹ The ensuing catastrophe was a catalyst for FDA reformation and legislation to safeguard patient interests.¹ Today, drugs must undergo intense preclinical studies before entering three-phased clinical trials, and require post-market monitoring to evaluate long-term benefits and risks.⁸

Mechanisms of teratogenesis

Due to its complex biochemistry, the exact pathway by which thalidomide induces embryopathy has not been established, although over 30 hypotheses have been proposed.³ The actual mechanism may be a combination of present models. Recent research has focused mainly on three of these models: anti-angiogenesis; oxidative stress; and, cereblon.

Anti-angiogenesis

Angiogenesis, the outgrowth of new blood vessels from pre-existing ones,⁹ is essential to the growth of developing limb buds. The DNA intercalation model suggests that thalidomide prevents the transcription of pro-angiogenesis genes by directly binding to their DNA promoter regions.¹⁰ CPS49, a thalidomide analogue, has been shown to reduce vessel density in chick limb buds via alterations of gene expression.¹¹ These include the suppression of fibroblast growth factors required for cell proliferation and limb patterning.⁵,¹¹ Interestingly, earlier exposure to CPS49 resulted in worse outcomes.¹¹ This could explain the spectrum of limb defects observed in humans, i.e., amelia (total absence of limbs), phocomelia (defective proximal limbs) and digit loss.¹¹

Oxidative stress

Thalidomide is bioactivated by embryonic enzymes to form a free radical intermediate.¹² This substance produces reactive oxygen species (ROS) that damage embryonic DNA and proteins.¹² Pre-treatment of rabbits with a free radical spin trapping agent before exposure to thalidomide reduces defects at birth.¹² Furthermore, Knobloch and colleagues demonstrated how ROS alters the Bmp/Dkk1/Wnt signalling pathway, which eventually promotes the apoptosis of progenitor cells that are critical for limb and eye developments.¹³

Cereblon

The recent discovery of cereblon (CRBN), the binding target of thalidomide, marked a major breakthrough in the understanding of its teratogenic effect.¹⁴ Thalidomide-CRBN binding inhibits ubiquitination, a process that marks substrates for degradation, causing them to build up and downregulate fibroblast growth factors.¹⁴,¹⁵ Introducing mutant CRBN⁵⁵⁸⁴⁴ with low affinity for thalidomide into zebrafish and chicks reduced thalidomide-associated defects in these species.¹⁴

Problem with animal models

Grünenthal's trials of thalidomide demonstrated a major downfall of drug testing in animals: the same drug can have different effects on different species. Thalidomide is teratogenic in rabbits, chicks and zebrafish, but not in mice, pigs or rats.¹⁶ Unfortunately, rats were the only species tested by Grünenthal.¹ Thalidomide needs to be metabolically activated to become anti-angiogenic; this seems to occur to a greater extent in humans and rabbits compared to rats.¹⁷ Rats also have more glutathione stores in their limb buds than rabbits, and so are better able to counteract oxidative stresses.¹⁴ Modern toxicological studies routinely assess drug effects in several species, including rodents and non-rodents. Still, human responses can never be fully predicted.

Evolving indications

Thalidomide’s titanic history did not sentence it to death. In 1964, Dr Sheskin, a dermatologist in Jerusalem, administered thalidomide to a man suffering from weeks of insomnia due to pain from erythema nodosum leprosum (ENL) – a complication of leprosy – after several other sedatives failed to put him to sleep.¹,¹⁸ Dramatic resolution of his insomnia – as well as (astonishingly) his pain, fever and cutaneous sores – prompted further study of thalidomide for the treatment of ENL; it received approval in 1998.¹⁸ Although better drugs have since been developed,⁶ this discovery kickstarted the new fate of thalidomide, and several new indications have since been discovered.

Major factors that initiated thalidomide’s re-emergence include the ineffectiveness of standard treatments, mainly in relapse settings.¹⁹ Additionally, certain disease characteristics can be targeted by its anti-angiogenic, immunomodulatory and anti-inflammatory properties.³ Thalidomide decreases tumour necrosis factor-alpha (TNF-α) and interleukin-12 production in monocytes and macrophages.¹⁸ This may explain its efficacy in diseases hallmarked by elevated TNF-α levels, including ENL.¹⁸ Thalidomide also inhibits the production of pro-inflammatory cytokines, co-stimulates CD8+ T-cells, promotes T-cell expansion and IFN-γ release, and induces a shift from Th-1 to Th-2 immune response.²⁰ Two classes of thalidomide derivatives – immunomodulatory drugs (IMiDs)²¹ and selective-cytokine-inhibitory drugs (SelCIDs)²² – were developed in recent years to enhance potency and avoid thalidomide-associated toxicities.²³ Clinically important IMiDs include lenalidomide/CC-5013 and pomalidomide/CC-4047.²¹ SelCIDs have not yet been widely studied clinically, but CC-7034 and CC-9088 have shown anti-tumour effects in murine cancers.²²
Haematological malignancies

Multiple myeloma (MM) is characterised by aberrant proliferation of bone marrow plasma cells, which leads to skeletal lesions, anaemia, hypercalcaemia, increased infection risk and kidney failure. Though MM is incurable, the survival rate has increased from 35.6% in 1998-2001 to 44% in 2006-2009 (in the US) partly due to the introduction of thalidomide and lenalidomide. Addition of thalidomide to a standard dexamethasone regimen shows significantly higher response rates (63%) than the dexamethasone only regimen (41%). Lenalidomide-dexamethasone is approved for relapsing and refractory MM, and plays a role in maintenance therapy. Thalidomide and IMiDs inhibit the growth and encourage the death of MM cells. The adhesion of normal bone marrow cells to MM cells via cell adhesion molecules (CAMs) elevates the local levels of vascular endothelial growth factor (pro-angiogenesis factor) and interleukin-6 (MM cell survival signal). Thalidomide and its derivatives reduce the expression of CAMs, partly by downregulating TNF-α. They also reduce the proliferation of MM cells by inhibiting DNA synthesis.

Cell death is promoted via two pathways – apoptosis by activation of caspase 8 via FasL and lysis by stimulation of natural killer cells (Figure 1). IMiDs are also useful in the treatment of myelodysplastic syndromes, a group of haematological conditions arising from bone marrow failure with a tendency to progress into acute myeloid leukaemia. Lenalidomide is the approved first-line treatment for low-risk patients with the del(5q) karyotype with anaemia, who are non-eligible for haematopoietic stem cell transplantation. In a Phase III study of patients fulfilling these criteria, 56% became RBC transfusion-independent (main treatment goal to prevent organ damage and iron overload) for ≥26 weeks following lenalidomide therapy. Recently, lenalidomide was approved for a new indication – mantle cell lymphoma, specifically in patients who are refractory to bortezomib or bortezomib-containing regimen and patients in relapse.

Non-haematological malignancies

Thalidomide and lenalidomide have limited roles in solid tumours. Phase I/II studies using these agents in castration-resistant prostate cancer showed exciting results with ≥50% serum reduction of prostate-specific antigen, the disease biomarker. Nevertheless, negative results from the Phase III MAINSAIL study of lenalidomide indicated the need for further analysis. In renal cell carcinoma, disease stabilisation was achieved with thalidomide alone, but with severe toxicities including lethargy, peripheral neuropathy, deep vein thrombosis and pulmonary embolism. Several combination immunotherapy and chemotherapy regimens have been studied; combination thalidomide/interleukin-2 treatment is potentially entering Phase III study for metastatic renal cell carcinoma.

Thalidomide/temozolomide has demonstrated some efficacy in malignant melanoma and glioblastoma multiforme. Disappointingly, little or no benefit was found for breast, ovarian, colorectal, hepatocellular, small-cell and non-small-cell lung carcinomas.
HIV-associated conditions

Oral aphthous ulcers, though normally self-limiting in healthy people, are progressive in patients with AIDS. Many groups have reported thalidomide’s activity in this disease.44 one group has achieved complete healing in 55% of the subjects.45 A Phase II study of Kaposi’s sarcoma showed a 40% response rate but did not replicate the peripheral blood reduction of Kaposi’s sarcoma virus (HHV8) seen in previous smaller studies.46 In AIDS-related wasting and diarrhoea, both associated with elevated TNF-α level, thalidomide induced weight gain and reduced bowel movements in affected patients.47

Dermatological conditions

Thalidomide’s success in the treatment of ENL inspired studies of its efficacy in diverse refractory dermatological problems. Case reports and small studies blossomed in the 1980s and showed exciting results for various conditions.48 Thalidomide has been effective in refractory actinic prurigo, prurigo nodularis, paraneoplastic pruritus and chronic discoid lupus erythematosus.49 Prolonged thalidomide treatment for sarcoidosis shows impressive rates of resolved cutaneous lesions.50 Accumulating data is suggesting that thalidomide should be the primary treatment for vulvar Langerhans’ cell histiocytosis, but further studies are required.51 The anti-inflammatory and immunomodulatory properties of thalidomide are most probably responsible for its dermatological activities.18 However, not all initially promising results have led to clinical use. Despite confirmed efficacy in Behcet’s syndrome, a systemic vasculitis characterised by recurrent uveitis, and oral and genital ulcers,52 significant side effects, especially a high incidence of deep vein thrombosis, prohibit thalidomide’s use in most patients.53 Recent studies of its use in chronic graft-versus-host-disease have disproved clinical benefits suggested by earlier research.54

Conclusion

Thalidomide has fallen and risen in favour over the past five decades. Since its disastrous introduction to the market as a sedative, and subsequent withdrawal, we have learned much about thalidomide, and appreciate some of the plausible mechanisms behind its teratogenicity.

We have learnt how to manipulate the drug for new applications; thalidomide and lenalidomide have improved the prognoses of MM and myelodysplastic syndrome and are widely studied in other areas such as dermatology and HIV-associated conditions. Nevertheless, teratogenicity and adverse effects still limit their clinical applications. We have also learned important lessons about the pharmaceutical industry generally, including the limitations of animal models in drug testing and the importance of stringent drug safety regulations.

With these lessons in mind, research on thalidomide’s therapeutic potential should continue. An exciting prospect is the development of analogues that preserve thalidomide’s beneficial activities without its toxicities. Meanwhile, new and existing combination therapies await further exploration. With these lessons in mind and bright prospects for the future, the resurrection of thalidomide can continue to benefit mankind without repeating its dark history.

References

15. Jefferys C. Regulation of protein levels and post-translational modification of proteins. [Lecture notes]. Royal College of Surgeons, Ireland; notes provided at a lecture given 2012 March 9.
Transvaginal cholecystectomy: a novel surgical technique

Abstract
Over the past 25 years, there has been a swift evolution of techniques for the performance of a cholecystectomy. In an effort to reduce pain, scar size and recovery time, laparoscopy has largely replaced the traditional open technique. Endeavours to eliminate surface scar formation and reduce postoperative pain have led to the development of natural orifice transluminal endoscopic surgery (NOTES). In NOTES a flexible endoscope is passed through an existing bodily orifice to reach the abdominal cavity. Transvaginal cholecystectomy (TVC) is the most commonly performed NOTES procedure. It involves accessing the abdominal cavity through a posterior colpotomy and using the vaginal incision as an operative port. TVC is a feasible operation when performed by senior surgeons highly trained in endoscopy. Issues such as surgical platform, spatial orientation, and technical challenge must be addressed before TVC is routinely practised. Patient preference, postoperative sexual function, and dyspareunia need to be thoroughly investigated. This review aimed to explore TVC in detail, as well as barriers to its widespread clinical use, and future implications.

Keywords: scarless surgery; transvaginal cholecystectomy; natural orifice transluminal endoscopic surgery.

Introduction
Cholelithiasis is one of the most common medical problems needing surgical intervention, affecting approximately 10% of the adult population in the US. Approximately 500,000 cholecystectomies are performed for symptomatic cholelithiasis every year. Known risk factors include female gender, obesity, increased age, multiple pregnancies, and certain ethnic groups.¹ Since the late 1980s, laparoscopic cholecystectomy has largely replaced laparotomy as the treatment of choice for symptomatic cholelithiasis.² Shorter recovery times and lower levels of trauma make it an attractive surgical approach to both doctors and patients. Complications of laparoscopy are few but include surgical wound infection, wound adhesions, postoperative pain, and scar formation.³ In recent years, attempts have been made to minimise the invasiveness of laparoscopic cholecystectomy with the goal of reducing postoperative pain and scar formation.⁴ Surgeons have reduced the size and number of abdominal operating ports, the size of instruments and, most excitingly, have introduced the use of flexible endoscopy.⁵⁻⁶
Performing a cholecystectomy using flexible endoscopy eliminates surface incision, which can theoretically reduce postoperative pain and wound infection while improving cosmesis and recovery times. This technique takes advantage of natural orifices to allow for endoscopic therapy. This procedure, called natural orifice transluminal endoscopic surgery (NOTES), has garnered a great deal of attention in the surgical community and is purported to be the next leap forward in minimally invasive surgery.\(^7\)\(^-\)\(^10\)

NOTES provides the potential for incisionless surgery, which has major implications for all surgical procedures, not just cholecystectomy. The first NOTES procedure was performed by Kaloo et al.\(^11\) at Johns Hopkins Hospital, Maryland, in 2005. This initial procedure sparked great interest and subsequent publications involving successful transluminal endoscopic surgeries. Transvaginal cholecystectomy (TVC) is an exciting novel procedure that represents a philosophical shift in the way surgery is performed. The feasibility of this procedure in everyday clinical practice is debated, and its superiority over the conventional laparoscopic cholecystectomy is questionable.\(^12\)\(^-\)\(^16\)

This article will describe a TVC procedure in detail, examine barriers to its widespread clinical use, and discuss future implications.

### Discussion

#### The procedure

NOTES can be performed by introducing an endoscope into any external natural orifice such as the anus, mouth, vagina or umbilicus to gain entry into various cavities (Figure 1). The transvaginal approach is currently preferred as there is a decreased risk of intestinal leakage and infection through the access site.\(^12\) Furthermore, gynaecologists and general surgeons have used transvaginal access for years with very good results.\(^13\)

Compared to other access points, the vagina is easily closed and has low risk of gastric or colonic fistula.\(^14\) Contraindications to vaginal access are listed in Table 1.

Bessler et al. performed the first TVC using no abdominal entry points (Figure 2).\(^15\) The patient was placed in the lithotomy position and strapped in. The table was then elevated and the patient put in steep Trendelenburg position to minimise risk of small bowel damage during surgery. A 1cm colpotomy was performed in the posterior fornix of the vagina. A 15mm port was passed through the colpotomy incision. This port allowed for insertion of endoscopic devices (Figure 3) and was left in the posterior fornix for the remainder of the surgery. Through the 15mm port, pneumoperitoneum was achieved.\(^15\) A 12mm double-channel therapeutic gastroscope was placed directly into the 15mm port. This gastroscope was then retroflexed to visualise the entry site and make sure no structures were damaged upon entry. A second colpotomy was made just lateral to the initial site and a 5mm trocar introduced. The 5mm trocar allowed for insertion of an extra long curved retractor. The retroflexed gastroscope was used to guide the entry of the curved retractor into the abdomen.\(^15\)

The curved retractor was used to grasp Hartmann’s pouch and the gallbladder was retracted upwards and laterally to expose the structures of the triangle of Calot. An endoscopic knife and grasper...
forceps were passed through the two channels of the gastroscope and used to dissect these structures. The cystic duct and artery were each clipped three times using modified endoscopic clips. The gallbladder was resected and removed through the 15mm trocar. The pneumoperitoneum was aspirated via the endoscope. The two trocars were removed and the colpotomies closed with a running stitch.

**Patient concerns**

For TVC to become an approved treatment the patient population must consider it a viable option. A recent survey of 300 women indicated that 96% expressed concerns before the procedure about sexual function and fertility.\(^16,17\) Bucher et al.\(^17\) suggest that this trepidation occurs because physicians are unable to answer questions regarding postoperative fertility and sexuality. A 2013 study\(^18\) conducted at Yale investigated quality of life and sexual function after TVC. The study suggests that sexual function remains unchanged and quality of life either is unchanged or improved one month after the procedure; however, the cohort was relatively small. There is limited published data regarding postoperative effects after TVC; however, there are many studies\(^19-22\) investigating sexual function after transvaginal hysterectomy. These studies found no negative effects and actually noted improvements in sexual function post procedure. It is questionable whether these results can be applied to TVC, a non-gynaecological procedure.

**Spatial orientation**

Unique issues with depth perception and anatomy recognition make learning and performing NOTES very difficult. In traditional laparoscopy, three or more abdominal ports are usually used, which preserves triangulation. In pure NOTES, where no abdominal ports are used, triangulation is substantially decreased. The problem of orientation and guidance in the abdominal cavity has been discussed in several review articles.\(^23-25\)

Researchers\(^26,27\) have attempted to address these issues by developing a novel magnetic guidance system that uses external magnets to steer and operate instruments. These instruments are inserted through the vaginal orifice and controlled externally by a large hand-held magnet. When the magnet is moved along the abdominal surface the instruments move to a different location in the abdominal cavity. This novel technique has challenges of its own. There are many reports\(^28-30\) of magnetic technology use in human cases. A large human study performed by Dominguez et al.\(^29\) reported no magnetic-related complications in 40 patients undergoing NOTES-assisted cholecystectomy. However, there are very few studies of actual tissue effects in humans. Best et al.\(^30\) reported mild blanching and petechiae of the porcine peritoneum after four hours of constant compression with the internal and external magnets.

**Surgical platform**

The current endoscopes are difficult to operate intra-abdominally, as they are designed for movement inside a lumen.\(^31\) These endoscopes are often modified gastrosopes with only a small number of working instrument channels, and are highly flexible. This flexibility is advantageous when passing through the lumen of the vagina and into the peritoneal cavity, but becomes problematic as it is too flexible intra-abdominally.\(^31\) When the target organ is reached, adequate retraction and dissection are extremely difficult as the working channels are small and few. A larger, stronger surgical platform with numerous working channels is crucial for a successful NOTES procedure.\(^32\)

There are several new instruments under investigation (Figure 4). A prototype called the ANUBISCOPE (Karl StorzEndoskope; Tuttlingen, Germany) uses a four-way articulating flexible endoscope with a 16mm articulating vertebrae section and an 18mm unique distal head (Figure 4a). The distal head has two movable arms with 4.2mm working channels. External to these arms are a pair of jaws that create
triangulation of the working channels. Perretta et al. have reported a successful TVC in 60 minutes using the ANUBISCOPE. The direct drive endoscopic system (DDES; Boston Scientific, Natick, MA, USA) is a multitasking platform that overcomes some of the limitations of current endoscopes (Figure 4b). The system consists of three working ports and a distal guide sheath that can accept a 6mm endoscope and two 4mm articulating instruments. It is unique because it allows the surgeon to operate instruments bimanually at the distal sheath and simulates a laparoscopic procedure. Thompson et al. used this novel multitasking platform to demonstrate triangulation, grasping, suturing and cutting. They concluded that complex endoscopic techniques that would normally be difficult, if not impossible, with standard endoscopes can successfully be performed using the DDES. An area of further research is robotised endoscopes in NOTES. This technology is still in the initial stages of development with few studies conducted. Robotic endoscopy aims to complement NOTES procedures by improving abdominal and peritoneal exploration while reducing postoperative pain and discomfort.

**Bridging the gap: laparoscopic-assisted TVC**

TVC is rarely performed, even in academic centres. The largest trial to date included only 551 patients. Many researchers believe that more prospective, randomised clinical trials are needed comparing natural orifice surgery with standard laparoscopy before TVC can be routinely practised. There are several ‘hybrid’ approaches that aim to ease the transition between laparoscopic surgery and pure NOTES procedures. These techniques combine transvaginal access with conventional abdominal ports. Hybrid procedures have been shown to reduce adhesion development, decrease postoperative pain, and lead to faster recovery times.

References


All in your head: is the use of placebos a form of benevolent deception?

Abstract
The study aimed to explore the view that the use of placebos is a form of benevolent deception, based on the evidence available.
A literature search was carried out using mainly electronic databases such as Ovid Medline, PubMed and The Cochrane Library. Scirus and Google Scholar were also used.
Placebo is Latin for ‘I will please’, and this is what it aims to do. For the purpose of this paper, placebo is defined as a pharmacologically inert medication, but the broader term ‘placebo effect’ and all that it encompasses is also explored.
A Cochrane Review found placebos to have a significant statistical effect on pain and nausea, using only quality-controlled studies. Although many placebo trials claim to significantly improve both patient- and observer-reported outcomes, a 2010 Cochrane review shows that most of these reports are founded on studies that have failed to randomise patients to placebo or no treatment groups, thereby reducing their reliability.
Although the placebo should not be considered a wonder drug, it can alleviate symptoms when applied to specific conditions such as pain. Significant ethical issues are yet to be resolved before the use of the placebo in clinical practice could be considered.

Royal College of Surgeons in Ireland Student Medical Journal 2013; 14: 46-48.
Introduction
The term ‘placebo’ is Latin for ‘I will please’, a translation which aptly describes the actual purpose of a placebo. The goal of the placebo is to elicit a positive response without the use of pharmacologically active medication. For the purpose of this article, placebo is defined as a pharmacologically inert medication, and ‘the placebo effect’ as an effect brought about without necessarily using medication, inert or otherwise. The history of the placebo is long and eccentric. The term originated in the 14th century, where it referred to hired mourners at funerals; even then it was used to describe pretence. In 1811, the revised *Quincy’s Lexicon-Medicum* defined placebo as “an epithet given to any medicine adapted more to please than to benefit the patient”.2 Until the 1950s, the perception of the placebo was that “it cannot harm and may comfort the patient”.3 The idea of the placebo is presented as a sort of panacea, but physicians are aware that it is only efficacious in limited circumstances. However, in the same way a cancer therapy would not be discredited for failing to cure migraines, all illnesses should not be grouped together when measuring the effectiveness of placebos.

All in your head: neurobiology of the placebo effect
In order to understand placebos and the placebo effect, we must consider their mode of action, or the neurobiological reactions they elicit. Results suggest that placebo-induced analgesia is mediated by the endogenous opioid system.4 In an experiment carried out using functional magnetic resonance imaging (fMRI), placebo-controlled analgesia was associated with decreased activity in pain-sensitive regions of the brain. It was also linked to an increase in activity in the prefrontal cortex, which modulated the experience of pain. MRI images clearly demonstrate the physiological effect of the placebo on pain response.5 Many studies link placebo analgesia with activation and heightened functioning within various areas of the brain and spinal cord. Conditioning and expectancy both play a role in this. The placebo effect can be achieved through classical conditioning, whereby both an actual stimulus and a placebo are used concurrently, until the placebo is associated with the effect from the actual stimulus.6 In our society, we are conditioned to associate tablets or injections with the alleviation of unpleasant sensations. Therefore, just the experience of taking a tablet or receiving an injection may allow us to believe that we have gained some symptomatic relief, even if this is not the case. An ‘expectancy’ effect is displayed whereby a placebo, believed to be an active medication, has an effect comparable to that of the active medication. Enhancement of the expectancy effect can be achieved through variables such as enthusiasm of the physician, use of particular sizes and colours of tablets, or alternative methods of delivery such as injections over tablets.7

The bright side
Placebos have been shown to alleviate many symptoms such as pain and nausea.8 In patients with depression, antidepressants and placebos have a similar effect on both the physiological mechanisms within the brain and on the patient-reported outcomes. A recent Cochrane review reported a small statistical difference between the efficacy of active antidepressants and of placebos. This difference was in favour of the active drug, but leads us to question whether the effect of the placebo is underestimated in the treatment of this condition.9 It was feared that using placebos in trials to test antidepressant medication might increase the risk of suicide. This proved to be untrue.10 It is worth noting that many of these studies were carried out before the widespread use of standardised diagnostic criteria and rating scales, so the severity of the depression in the studies is unknown. During clinical trials, new drugs frequently fail to pass efficacy tests because of the placebo eliciting almost as positive a result as the drug itself. This has led some medical professionals to argue that many compounds used as active medications may be only slightly more sophisticated than the placebo.

How reliable are the results?
Although many placebo trials claim to significantly improve both patient- and observer-reported outcomes, a 2010 Cochrane review showed that a lot of these reports on the effect of the placebo are based on studies that failed to randomise patients.8 Variations in the effect of the placebo were partly explained by differences in how trials were conducted and what information patients received. Patient-reported outcomes can be positively influenced by treatment with a placebo, but differentiating between valid patient-reported outcomes and biased reporting is complex. Although pain is one of the symptoms that placebos have been shown to alleviate, there is still considerable heterogeneity between results of studies reporting on this effect, even among trials with low risk of bias.8 Pharmacologically inert substances may also cause harmful effects when taken by patients; this is termed the ‘nocebo’ effect. Like the placebo effect, the nocebo effect is thought to be influenced by subconscious conditioning and by the expectancy effect.11 If the expectation of a positive outcome increases its likelihood, it is only fitting that negative expectations function in the same way. A history of adverse reactions to drugs can be correlated with an increased rate of future nocebo effects. In a study of 600 patients whose medical history included adverse drug reactions, 27% developed side effects when given the pharmacologically inert placebo.12

Ethical dilemma
Treating patients using a placebo presents a huge ethical dilemma. There is a long-running debate about whether placebos should be used in clinical practice, as well as in treatment trials. Many articles have been published supporting both sides of the argument.13 Patients have the right to know what medication they are taking. When prescribing a placebo, if the nature of the treatment is not
Placebos are a necessary part of medical research. In studies involving a disorder for which there is an available, effective treatment, a placebo arm of the trial would be unethical. For many studies, however, comparison with a placebo is integral to drawing a conclusion on the validity of the results and the efficacy of the treatment. 

The axiological deviation between placebo use in clinical trials and treatment, with full disclosure that, although pharmacologically inactive, may alleviate their symptoms. The negativity associated with the word placebo could be avoided, while still making use of it. Conversely, there is the argument that it is not ethical to abstain from the use of placebos when we know that they have a marked impact on some conditions, such as anxiety. If a placebo can aid in a patient’s treatment, when paired with an empathetic physician, it may be unethical to withhold this treatment.

Conclusion
Care should be taken not to resort to using placebos as a replacement for what could be achieved by a positive doctor-patient relationship. Although the placebo has proven to alleviate some symptoms, most of the placebo effect can be achieved without the use of a physical placebo pill. Treatment isn’t as linear as prescribing the patient medication and sending them home. As Hippocrates advised, physicians should “heal occasionally, relieve often, and comfort always”. The placebo has potential as a clinical intervention, but there are important ethical issues that must be appropriately addressed. One way of overcoming the mistrust surrounding placebos would be to rename them. The term in itself is reactionary, intrinsically associated with dupery and deceit. Patients could be prescribed an inert replacement for what could be achieved by a positive doctor-patient relationship.

Physicians should “heal occasionally, relieve often, and comfort always”. Placebos can be considered a form of benevolent deception, but the repercussions of prescribing them have the potential to be far from benign.
Physiological mechanisms underlying exercise prescription non-compliance in patients with type 2 diabetes mellitus

Abstract
Type 2 diabetes mellitus (T2D) is a growing epidemic worldwide. One of the key treatments for T2D is exercise. Exercise has been shown to have positive effects on many aspects of the disease including improving serum glucose levels and insulin sensitivity. Unfortunately, patients with T2D tend to have poor compliance with exercise regimes. A number of reasons for the failure of exercise programmes have been suggested. This article aims to explore some of the possible explanations, and to outline future directions in this area of research.
Introduction
Type 2 diabetes mellitus (T2D) is one of the fastest developing worldwide epidemics. There are currently nearly 300 million people suffering from this disease.\textsuperscript{1} It has long been known that physical activity is one of the cornerstones of the management of T2D.\textsuperscript{2} However, it is also recognised that persons with T2D have low adherence to exercise programmes, even when prescribed by doctors.\textsuperscript{3} This has been attributed to poor exercise tolerance by people with T2D.\textsuperscript{4} It has been suggested that a number of physiological mechanisms could contribute to this exercise intolerance, such as an impaired cardiac response to exercise, a deficit in the skeletal muscle diffusion, or impairments in oxygen delivery (Figure 1).\textsuperscript{5} The current primary focus of investigation is the possibility that impaired oxygen delivery may underlie this poor exercise tolerance. This review will attempt to explain the mechanism of non-compliance in patients with T2D and potential future areas of research and treatment.

Exercise as treatment for T2D
While there are a number of pharmacological interventions that can be prescribed for patients with T2D, it is recognised that one of the ideal treatment methods is physical activity.\textsuperscript{2} Physical activity has been shown to target many of the major symptoms of T2D. For example, exercise has been shown to reduce blood glucose levels,\textsuperscript{6} elevate insulin sensitivity and insulin-independent muscle glucose uptake,\textsuperscript{7} and mitigate the insulin resistance that exists in patients with T2D. It has been demonstrated by a number of research groups that patients with T2D who exercise also have lower resting and submaximal exercise heart rates, increased stroke volume and cardiac output, enhanced oxygen extraction, and lower resting and exercise blood pressure.\textsuperscript{5,8} While it is generally recognised that physical activity is highly effective for the management of T2D, many patients have difficulty adhering to the exercise prescription given to them by their doctors. In one study by Thomas et al., only 34% of patients with T2D performed any kind of exercise, and of those only 9% performed sufficient exercise to cause a “large” change in heart rate or breathing.\textsuperscript{9} The authors found that the most significant barrier to performing physical activity was a lack of confidence in being able to perform the exercise and feelings of “tiredness.”\textsuperscript{9} Interestingly, it has been demonstrated that higher levels of glycosylated haemoglobin (HbA1C) correlated with a lower exercise capacity in patients with diabetes.\textsuperscript{10} Thus, there may be a physiological mechanism underlying the exercise prescription compliance issue in people with T2D.

Exercise intolerance in patients with T2D
A number of physiological mechanisms could be responsible for this exercise intolerance, such as an impaired cardiac response to exercise, a deficit in the skeletal muscle diffusion, or impairments to oxygen delivery.\textsuperscript{5} Current research is focused on the impaired convective oxygen delivery theory. Of these studies, there are two main categories of investigation: those addressing muscle blood flow during the transition to exercise; and, those addressing steady-state exercising muscle blood flow.

Blood flow during transition to exercise
When exercise is initiated, an oxygen deficit becomes established, which forces the body to compensate by increasing flow either through increased pressure or increased vasodilation. However, if there is a defect in these responses, as has been established in people with T2D, the body cannot compensate, resulting in early-onset fatigue. One study has established a decreased kinetic response in people with T2D compared to obese controls,\textsuperscript{4} while other studies have shown that there is a greater reliance on oxygen extraction in an attempt to compensate for this initial...
Although there are few studies looking into the responses to decreased muscle blood flow at the onset of exercise in patients with T2D, their conclusions are clear: there is a reduced kinetic oxygen uptake response in patients with T2D during the transition to exercise.

Steady-state exercise blood flow
In addition to failed recovery of initial oxygen deficit, T2D causes significant reduction in steady-state exercising muscle blood flow. Of particular note is a 2003 study by Kingwell et al., which demonstrated an impaired blood flow response in the legs during cycling exercise in subjects with T2D when compared to age- and weight-matched controls. This was due to increased vascular resistance, which persisted despite raised blood pressure. Another study demonstrated a 25% reduction in blood flow that was independent of cardiac output, suggesting that the major complication in subjects with T2D was related to a reduction in vascular function. Taken together, these two studies point to an impaired ability to dilate the peripheral vasculature in response to exercise, that is, a reduction in the capacity to increase vascular conductance in response to increased metabolic demand. This could be due to impaired vasodilation, increased vasoconstriction from the sympathetic nervous system, or a combination of both.

Impairments to vasodilation
Normally, there are several receptor types lining the endothelial wall. These respond to circulating mediators such as adenosine triphosphate (ATP), nitric oxide (NO) and prostaglandins, to cause both local and upstream (towards the originating artery) vasodilation. This increases vascular conductance and improves overall blood flow (Figure 2). However, this process may not function normally in patients with T2D. Several studies have focused on the function of endothelial-dependent vasodilatory capabilities of patients with T2D. For example, Sprague and colleagues have demonstrated a reduced erythrocyte release of ATP, thus reducing ATP-mediated vasodilation. Normally ATP released from red blood cells binds to purinergic receptors on the
luminal surface of the endothelium and catalyses the production of NO, a major upstream vasodilator.16 Erythrocyte release of ATP is reduced in patients with T2D, which impairs the NO cascade. Similar results have been demonstrated for other vasodilatory mechanisms. However, this might not be the only contributor to vascular conductance – there may also be an increase in sympathetic activity, which increases systemic vascular resistance. In normal muscle, there are two factors governing oxygen delivery to muscle – arterial pressure and vascular resistance. In order to facilitate the increase in blood flow at the onset of exercise, arterial pressure must increase, vascular resistance must decrease, or a combination of the two must occur. Generally, an immediate increase in local vasodilatory factors increases vascular conductance, which increases the overall blood flow to the muscle.17 However, when the vascular conductance has reached its peak, the heart must play a greater role in maintenance of blood flow.18 By increasing cardiac output, the heart increases the mean arterial pressure, which has the effect of conducting more blood through the dilated artery in the muscle. There must be a balance between systemic vascular conductance and cardiac output in order to maintain arterial pressure. A problem arises when blood pressure is not sufficient to maintain the perfusion of exercising muscle. If this occurs, a secondary response termed the ‘muscle metaboreflex’ (MMR) acts to increase perfusion pressure and blood flow to the exercising muscle by reducing the conductance to other muscles.5

Muscle metaboreflex
The MMR is an exercise-induced pressor response that is activated during moderate- or high-intensity exercise (Figure 3). It involves a gradual increase in muscle sympathetic nervous activity (MSNA) during exercise, which differs from the almost immediate increase of heart rate and arterial pressure described above. It is thought to be a chemically stimulated feedback pathway that increases vasoconstriction and elevates mean arterial pressure during exercise.18 This increase in sympathetic vasoconstriction seems counter-intuitive, as it causes vasoconstriction in muscle that requires increased blood flow; however, complex mechanisms actually allow for increase in mean arterial pressure and therefore flow. Contracting muscle produces a number of metabolic by-products that accumulate in the blood, such as lactate, inorganic phosphate (Pi) and potassium.19 Some of these metabolites, including H+ and potassium, activate the free-ends of group IV muscle afferents, which have central nervous projections.20 The activation of these group IV muscle afferents results in an increase in their firing rate. This information is processed at the level of the nucleus tractus solitarii in the medulla, the site of the cardiovascular control centre, which responds with an increase in sympathetic efferent activity in the form of systemic MSNA.21,22 This leads to vasoconstriction in, and therefore reduced flow to, all major tissues, including the exercising muscle. By reducing the overall conductance to tissues in the body, there is a subsequent increase in mean arterial pressure.21,22 An advantage is only gained if vasoconstriction is caused in all other tissues except the exercising muscle – vasoconstriction at the exercising muscle would be counter-productive. To take advantage, there are two pathways that reduce the effect of vasoconstriction at the level of the exercising muscle: vasoconstriction and sympatholysis (the exercise-induced blunting of the MSNA).18 At higher intensities of exercise, the release of vasodilators counteracts the vasoconstricting effects of elevated MSNA from the MMR.18 Some of these vasodilator substances, including ATP, also blunt the effects of the MSNA at the level of the free-nerve ending.18 ATP activates vascular smooth muscle cell potassium channels that modulate the activity of the alpha-adrenergic vasoconstriction.23 The combined effect of vasodilation and blunted constriction protects vascular conductance to the exercising muscle at a level sufficient to benefit from the increase in mean arterial pressure.24 Thus, the maintenance of vasodilation in the exercising muscle coupled with the metaboreflex-induced increase in arterial pressure, leads to an increase in flow to the exercising muscle and thus an increase in oxygen delivery. However, if there are defects in either vasodilation or sympatholysis, as occurs in people with T2D, exercising muscle blood flow may be reduced.

MMR overactivity in T2D
There is a significant reduction in mitochondrial volume and electron transport chain function in diabetic muscle when compared to obese or lean controls.25 This altered morphology exaggerates the MMR. This means that these individuals rely more heavily on glycolytic and aerobic enzyme pathways. Because the onset of the MMR is governed by the production of metabolites such as H+, it is important to identify the methods by which these substrates are produced. The ‘net drive hypothesis’ describes the ability of the muscle to produce ATP through the collective contributions of oxygen \(P_{\text{cellO}_2}\), the phosphate energy state of the cell and the redox energy state (Figure 4).26 If any of these factors is decreased, there is a compensatory increase in the others in an effort to maintain ATP production sufficient to meet the demand of the muscle.26 If we consider that there is an oxygen deficit at the onset of exercise in T2D, then there must be a subsequent increase in both redox state and phosphate energy state in the myocyte. Thus, the onset of the MMR occurs at lower exercise intensities in an individual with T2D compared to a healthy individual. This would cause an increase in vasoconstriction and could result in the impairment to blood flow, contributing to the exercise intolerance that has been demonstrated in patients with T2D.
In addition to decreased ability to appropriately dilate the peripheral vessels, patients with T2D may have higher baseline MSNA, which, when coupled with MMR-induced MSNA, creates an overly vasoconstricted state in response to exercise. As a result, the MMR, which generally acts as a flow-restorative mechanism in healthy individuals, might in fact be self-defeating in patients with T2D and lead to the exercise intolerance that makes management of this disease so difficult.
Conclusion

Exercise is a vital prescription for the treatment of patients with T2D – it can lower blood glucose, improve insulin sensitivity and target many of the complications of T2D. However, the difficulty for this population is that there is a solid physiological basis for early-onset fatigue in people with T2D. This has clinical implications for the prescription of exercise as a method of treatment; physicians must be mindful of potential additional requirements such as exercise aids, more manageable exercise regimes, or alternative therapies that might ameliorate this deficit.

Further research into the significance of the MMR and its potential contributions to exercise fatigue in this population will elucidate ways to combat this oxygen deficit, and make the exercise prescription more tolerable and thus feasible for the T2D patient population.

References

The foetal origins of adult health

Abstract
Life course epidemiology examines the biological, behavioural and psychosocial processes that operate throughout an individual’s life and influence the risk of disease. This approach is based on the foetal origins hypothesis, which examines how early life exposures can have long-term effects on adult health. This theory emerged from research that demonstrated the association between low birth weight and cardiovascular disease in adults. However, many criticisms were raised, as these initial studies did not provide a biological explanation for this association. More recently, animal and human nutritional studies have provided putative mechanisms linking the irreversible changes that occur during the perinatal period to adult health. Further, epigenetic studies have also provided support for the foetal origins hypothesis, as it has been demonstrated that permanent structural DNA modifications can occur early in life. Importantly, there are several methodological issues at play that challenge the life course study design, and the interpretation and relevance of results must be discussed. This article will explore the development of the foetal origins hypothesis and examine its supporting evidence, as well as discussing the methodological constraints and applications of this approach.

Introduction
What if birth weight could predict disease risk in adulthood? Research suggests that environmental conditions during the perinatal period may result in biological changes that predispose individuals to develop chronic disease as adults. This theory, known as the foetal origins hypothesis, is gaining momentum in the scientific community and reflects our growing knowledge of the complex aetiology of chronic disease. An emerging approach known as life course epidemiology aims to test this hypothesis.

A life course approach
Central to the life course approach is the idea that early social and physical environments alter biological development and result in long-term health implications. From conception through to adulthood, individuals will undergo phases of development known as critical and sensitive periods. Insults occurring during critical periods have irreversible consequences, such as those occurring during conception and organogenesis; however, insults occurring during sensitive periods, such as during the perinatal period, childhood and puberty, can be modified over time. In order to determine the particular environmental factors that affect these developmental periods, life course epidemiology integrates psychological, cognitive and biological research.
study conducted in England, Scotland and Wales from 1855 until 1930 investigated mortality rates by year of birth.\textsuperscript{3} Predictably, the authors found that all cause mortality rates improved with time, which likely reflected improvements in living conditions and healthcare. However, the authors also noted that despite these improvements, mortality rates for a given birth cohort remained the same throughout the lifetime of that cohort. In other words, regardless of exposure to improved living conditions, the mortality of a given cohort was not altered. While further investigation would be needed to draw any conclusions about the impact of the perinatal environment associated with the year of birth and subsequent adult mortality, the authors brought attention to their finding, known as a cohort effect, and offered broad explanations for it. They suggested that the perinatal environment is an important determinant of future mortality and that conditions later in life may only minimally impact adult health.\textsuperscript{3} By the 1950s, the potential for early life exposures to impact lifelong health was gaining momentum as a theory, but little had been done to explore the effect of these influences during development. Dubos et al. were among the first to use animal models to investigate the importance of maternal nutrition during the perinatal period.\textsuperscript{4} In identical environmental conditions, two groups of pregnant mice were fed either optimal or suboptimal diets until delivery, at which point both groups received the optimal diet. The mothers and their young were then examined over time. Offspring whose mothers were fed the suboptimal diet prenatally, weighed less at the time of weaning than the offspring of mothers fed the optimal diet. This weight difference was maintained over time, despite switching to the optimal diet post partum and maintaining identical environmental conditions. Exposure to a sub-optimal diet had a significant impact on morbidity and mortality, as the offspring demonstrated decreased efficiency of food utilisation, resistance to infection and lifespan, compared to those fed the optimal diet.\textsuperscript{4} Additionally, a later study used the setting of the Dutch famine of 1944-1945 to retrospectively investigate the effects of maternal starvation during pregnancy on the mental status of offspring in adult life.\textsuperscript{5} Near the end of World War II, the Nazis imposed a transport embargo on German-occupied Western Holland in response to Dutch refusal to co-operate. The severe winter that year froze the canals and no food reached the area. Food rations were distributed and, at the lowest point of the famine, intake was restricted to 450 calories per day.\textsuperscript{5} The authors reconstructed birth cohorts in this setting to determine how foetal age at famine exposure affected mental status 19 years later. Measures of mental status included intellectual quotient (IQ) and degree of intellectual disability. The findings from this study did not support the authors’ hypothesis that mental status is associated with famine exposure during the perinatal period. However, the authors did note a strong positive association between IQ and social class. The authors suggested that despite the lack of support for perinatal famine exposure and mental status, other environmental factors in childhood related to low social class, such as poor education and living conditions, might have long-lasting effects on mental development. Overall, the authors concluded that, while the perinatal period is a crucial developmental time, the environment in which a child is raised is also of great importance in determining mental development.\textsuperscript{5}

The foetal origins hypothesis

While not the first to recognise the importance of the prenatal environment on long-term health outcomes, English physician David J. Barker famously brought attention to the foetal origins hypothesis. In the late 1980s, Barker observed that the poorest regions of England and Wales had the highest rates of coronary artery disease (CAD), and that areas of high perinatal mortality were also those of predominantly low socio-economic status and poor living conditions. He hypothesised that physical and psychosocial stressors in this environment may affect developmental periods of growth and manifest as low birth weight. If exposure to stressors during critical and sensitive periods is associated with increased risk of disease later in life, then babies born with low birth weight may have increased risk of CAD. To test this theory, Barker and colleagues obtained birth records from these areas and located these individuals as adults. They found that men with the lowest birth weights had the highest mortality from CAD; additionally, weight at one year of age and CAD were inversely related.\textsuperscript{6} Barker’s work faced criticism for several reasons. To begin with, his study lacked biological plausibility because he could not describe a mechanism linking early life conditions to cardiovascular disease. Additionally, interpreting birth weight as a marker of foetal growth is flawed, even when adjusting for gestational age. Several pathways could result in low birth weight, but without detailed information about prenatal growth, it is impossible to know exactly when the growth restriction occurred. For example, growth restriction during the first trimester may have more devastating effects than during the third trimester, but both could result in low birth weight. Furthermore, because of the time elapsed between the perinatal period and adulthood, it is almost impossible to account for the many anthropometric, biological, behavioural, or psychosocial variables that could confound the results over time. Finally, Barker’s work was thought to undermine public health interventions that had traditionally focused on minimising disease by targeting adult risk factors.

Despite initial criticism, Barker’s observations have been replicated in several studies. The Helsinki Birth Cohort Study included 4,630 men born in Helsinki University Hospital between 1934 and 1944, and has been used to investigate foetal growth parameters on health and disease.\textsuperscript{7} The study found that low birth weight was associated with CAD; men with the lowest birth weights (<2,500g) had the highest hazard ratios of CAD. A slow rate of growth, which was determined by low BMI at one year of age, was also associated with an increased risk of CAD – an effect that was independent of birth weight. However, compensatory growth (low BMI at two years and high BMI at 11 years) was also associated with increased risk of CAD. All three variables – low birth weight, low BMI at one year, and increased compensatory growth – were associated with type 2 diabetes in adult life. These findings have been replicated in the United States,\textsuperscript{8} Sweden\textsuperscript{9} and India.\textsuperscript{10}
Mechanisms
Much of our knowledge about the association between low birth weight and CAD arises from studies exploring perinatal nutritional status and infant development. Two biological explanations propose mechanisms for this association: phenotypic plasticity and compensatory growth.11 Phenotypic plasticity occurs when a single genotype gives rise to various phenotypes. This phenomenon is evidenced by several animal studies, which demonstrate that minor changes in the nutrition of pregnant animals can produce permanent changes such as altered blood pressure, and changes in glucose regulation and lipid metabolism.12,13 Compensatory growth, where a period of suboptimal nutrition is restored and followed by a period of growth acceleration, is also suspected to link birth weight to CAD in adulthood. It is thought that low birth weight infants lack muscle due to growth restriction during a critical period of muscle development. If infants gain weight rapidly to compensate for their low birth weight, they are more likely to accumulate fat rather than muscle. This may lead to excess fat mass later on in life and predispose these individuals to CAD.14 Kidney growth is also thought to contribute to this phenomenon where low birth weight infants have smaller kidneys and reduced numbers of nephrons, which may predispose these individuals to hyperfusion and eventually to glomerular sclerosis and hypertension.15,16 Finally, liver function has also been implicated. The liver remains plastic until around five years of age; growth during this time may affect liver function permanently, resulting in lipid dysregulation.17

Epigenetics
In addition to the biological mechanisms outlined, the foetal programming hypothesis has led to an interest in epigenetics. Epigenetics refers to heritable genetic changes that are not coded in the genome, but are regulated by structural DNA modifications. DNA methylation, acetylation of histone proteins and synthesis of non-coding RNAs inhibit gene expression and are examples of epigenetic mechanisms.18 The insulin-like growth factor II (IGF2) gene plays an important role in human growth and development. This gene has received attention as a possible explanation for the link between abnormal foetal growth and metabolic disorders in adulthood. IGF2 is known to be maternally imprinted where only the paternal allele is expressed19 and hypomethylation of the differentially methylated region (DMR) leads to bi-allelic expression of IGF2.20 A 2008 study by Hejimans et al. investigated whether prenatal exposure to famine was associated with persistent changes in the IGF2 DMR.21 Once again, in the setting of the Dutch Famine of 1944-1945, the authors looked at periconceptional and late gestational exposure to famine in same-sex siblings, as well as unexposed births during this time. The authors hypothesised that imprinting of IGF2 DMR may be impacted by nutritional status in early gestation, which may result in hypomethylation and subsequent bi-allelic expression of IGF2 DMR. Furthermore, they suspected that, because this epigenetic change is permanent, this effect would be detectable during the time their study was conducted, six decades later. Indeed, the study found that individuals who were exposed to famine prenatally demonstrated a significant reduction in DNA methylation, compared to their unexposed, same-sex siblings. This finding provides strong evidence that prenatal environmental influences can impact critical periods in development and that these changes can have long-lasting effects.

Life course study design
There are several methodological issues inherent in the life course approach. First of all, cohorts must be followed from birth into adulthood. This can only be facilitated through the use of extensive resources that minimise loss to follow-up during the long period between exposure and disease. Furthermore, when such an extensive time period has elapsed between exposure and outcome, it is difficult to rule out confounding factors that may lead to erroneous conclusions about the relationship between the exposure and the outcome of interest. Another complicating issue is that our ability to observe the prenatal period is extremely limited and more reliable markers of perinatal growth, other than birth weight, must be established. Overall, the life course approach necessitates data that includes maternal information and repeated observations of exposures of interest over time, which can be extremely costly. Two study designs are commonly used in life course epidemiology. First, the new experiment looks at events such as earthquakes or famines, where people are naturally selected into exposed and unexposed groups.22 A historical cohort can be reconstructed retrospectively from such events, as was done in the Dutch Famine Study.21 and health outcomes can be assessed. This method may rely on medical records, but may also use self-reported information, which may introduce recall bias, especially if the study is conducted retrospectively. In a historical cohort, temporality may also be an issue, because it is difficult to prove that a given exposure occurred prior to, and actually resulted in, a negative health outcome. Another relevant life course study design is a prenatal cohort with archived biological specimens. Women in this type of study are enrolled during early pregnancy, biological samples are archived for later analysis and the children of the mothers are followed into adulthood. This approach achieves temporality (exposure occurred before the outcome), collects detailed behavioural and health information, and allows for the assessment of multiple exposures. However, this type of study is extremely expensive to conduct and must allocate sufficient resources to prevent attrition of the enrolled population over the long study period.1 Studies using these types of cohorts can be conducted retrospectively to increase efficiency and cost effectiveness, but rely on the availability of sufficient data.

Public health implications
The importance of the perinatal environment has been demonstrated in relation to CAD,5,7 body size24,25 and diabetes,25,26 and has even been implicated in the development of psychiatric conditions, such as schizophrenia.27-29 Life course has also brought attention to the accumulation of stressors over the lifetime, or allostatic load, which can contribute to poor adult
health. Notably, these effects are disproportionately seen among groups of low socioeconomic status, as this population is more likely to live in resource-scarce environments, be less educated, and have limited access to healthcare.10,31 The wide-scale public health implications of these findings must be determined and employed to shape health policy. If the perinatal environment is an important risk factor in chronic disease risk, perhaps such recommendations should focus on improving access to perinatal care, especially among vulnerable groups. Until the research becomes conclusive, the life course approach should be used to further gain insight into the complexity of chronic disease and its foetal origins.

References

Sleep-deprived doctors and patient safety: an unresolved link

Abstract
In autumn 2013, Ireland’s non-consultant hospital doctors went on a 24-hour strike to protest at the Health Service Executive’s lack of compliance with the European Working Time Directive. This paper reviews the literature regarding the relationship between sleep deprivation, doctor performance and patient safety. Detrimental effects on doctor performance, including cognitive ability and in real and simulated surgery, have not been clearly demonstrated. However, the long-term effects of sleep deprivation on doctor health and burnout remain unclear. Relatively few strategies, ranging from changes to scheduling programmes to pharmacological interventions, have been investigated to manage sleep deprivation more effectively. Ultimately, more long-term research is required to elucidate the link between sleep deprivation and patient safety.

Introduction
A serious prescription error and subsequent fatal drug interaction led to the death of 18-year-old Libby Zion in New York Hospital in 1984. This incident brought sleep deprivation and the long hours worked by medical interns to the forefront of public attention. It was Libby’s father, Sidney Zion, a lawyer and journalist, who took the hospital to court. As a result, a panel of experts known as the Bell Commission convened to review medical training and education in New York. One of the most important proposals to come out of this panel was the working hours limitation in 1989, which restricted residents to 80 hours per week and no more than 24 consecutive hours. However, the Accreditation Council on Graduate Medical Education (ACGME) only made this mandatory for resident training programmes in the USA in 2003. More recently, in July 2011, the ACGME limited postgraduate year one trainees to 16 hours of call, based on recommendations from the Institute of Medicine. Sleep deprivation is not an issue restricted to American medical residents; in autumn 2013 in Ireland, non-consultant hospital doctors (NCHDs) went on a 24-hour strike to protest at the lack of compliance with the European Working Time Directive (EWTD) by the Health Service Executive. In a letter to the Annals of Surgery, executive director of The American Board of Surgery Frank R. Lewis suggests that Libby Zion’s death did not result from sleep-deprived doctors, but rather from residents with too much responsibility and not enough senior supervision. Despite this evidence, he states that on the one hand, 80-110 hours per week is an extremely heavy workload and that if doctors are sleep deprived and have impaired judgement, patient safety may be endangered. On the other hand, he said that decreasing hours can reduce the clinical experience of residents and disrupt the continuity of patient care. In the balance is patient health and safety, both of which are paramount to the medical profession. Perhaps, then, the relationship between sleep deprivation, performance, and patient safety in medical professionals and students is not as unambiguous as we would immediately believe. This paper examines the literature to date.

Sleep deprivation and performance
Many tasks, including driving a car and flying a plane, are significantly affected by disruption of sleep schedules. However, studies examining the effects of sleep disruption on medical management and surgical task performance have turned up mixed results. In a prospective study by Halbach et al., there was significant decline in the cognitive function of medical students and residents pre and post call. In Ireland, working consecutive, long hour shifts negatively affected cognitive functioning, attention, information processing, and motor skills among junior doctors. Conversely, in a similar study looking at the effects of different styles of call (call every fourth night or a week of 12-hour ‘night float’ shifts) on third-year American medical students, there was no change in cognitive function pre and post call. The authors of this study point out, however, that cognitive function does not necessarily assess judgment and decision-making – both very important to any physician. In addition, the study participants were all medical students who may not experience the same amount of fatigue as on-call doctors making decisions throughout the night.

Simulated surgery
Using verified outcome measures such as the Epworth Sleepiness Scale (ESS) and the National Aeronautic and Space Administration – Task Load Index (NASA-TLX), which determines subjective workload, Tomasko et al. determined that a 24-hour call period preceding a simulated laparoscopic surgical task had no effect on learning a new technique or applying a previously learned technique in medical students. However, call was associated with a higher subjective workload, which could detrimentally affect the ability of doctors to deal with unexpected events, i.e., bleeding vessel during surgery, and emotional stress. In a randomised controlled trial by Uchal et al., voluntary surgeons and nurses were assessed on a laparoscopic physical simulator (suturing a perforated ulcer) after a 24-hour duty.
As the author readily suggests, however, the results may not be representative of what chronic fatigue might eventually lead to with regard to effects on surgical performance. In another study using an Eyesi surgical simulator, nine residents were assessed at three different times – pre call, post work and post call – in a simulated ophthalmic anterior segment surgery, and evaluated on number of performance errors. There were no differences in the number of performance errors.

Sleep deprivation and patient safety

Although the association between sleep deprivation and performance remains controversial, an important aspect of sleep deprivation is its effect on patient safety and outcomes. In a study by Landrigan et al., medical interns made 36% more medical errors (including serious medication and diagnostic errors) if they worked consistent 24-hour shifts when compared to shorter shifts. Emergency doctors on night shifts tended to make more mistakes as the night continued, were slower at intubating a mannequin, and were more likely to place patients incorrectly in a triage test at the end of the shift when compared to doctors working day shifts. Conversely, Mitchell and colleagues looked at the root cause analysis of sentinel events (major medical errors) in a health system in Dallas and found no association with resident fatigue.

Surgical outcomes

A retrospective study at the University of Virginia, which looked at over 6,000 cardiac procedures performed by attending cardiac surgeons over nine years, found no association between surgeon fatigue and patient morbidity and mortality. In an analysis of appendectomies and cholecystectomies performed at night (after a 16-hour shift) versus during the day by residents at Harbor-UCLA Medical Center, there were no differences in complication rates, length of operation or conversion in these common surgical procedures.

Sleep deprivation and doctor safety, health and education

Sleep deprivation can also have a significant effect on doctor safety. Residents are more likely to fall asleep at the wheel of a car when driving home after a call shift. Post-call residents are at significantly increased risk of needlestick injury. Mental health may also be negatively affected by sleep deprivation; according to Babson and colleagues, sleep deprivation increased the reporting of symptoms of anxiety, depression, and general distress in adults recruited from the general population. Sleep is important for maintenance of general health; doctors who do not get the appropriate amount of sleep can go on to develop chronic conditions, putting significant strain on the healthcare system in the future. Interestingly, although burnout, which is defined as the feeling of long-term, emotional exhaustion and reduced interest in work, is a common problem among medical trainees at the beginning of training, one study showed that excessive sleepiness based on the ESS was not correlated to burnout, but rather to personality type.

Strategies to reduce sleep deprivation

The difficulty in addressing sleep deprivation lies in balancing three parameters: patient care; resident education; and, resident satisfaction/stress. No resident training programme or call schedule has successfully done so, thus far. One of the main strategies proposed to reduce sleep deprivation is simply to reduce working hours. However, to date the evidence behind the reduction of work hours and improving patient outcomes has been inconclusive. A study looking at the 2011 work hour restrictions by the ACGME (16 hours for first-year residents) found that although residents were more well rested, they found they suffered increased work compression (doing the same amount of work in a shorter amount of time). The authors concluded that programmes should adapt their schedules to decrease work compression. Night float is a type of call schedule where doctors...
are assigned to work a shift, but not necessarily to a specific ward, and instead ‘float’ to whichever team requires them. In a study by Matthews et al., students subjectively felt more alert for clinical duties while on night float. In another study, Ray et al. looked at the use of modafinil, a wakefulness-promoting drug used in narcolepsy or shift work disorder, as an effective pharmacological countermeasure to one night of sleep deprivation and reduction in cognitive decline. The authors, however, do not state that this should be considered as a strategy for chronically sleep-deprived residents, as long-term effects of using these countermeasures are unknown.

Conclusion
The recent action by NCHDs in Ireland demonstrates the widespread importance of limiting the work hours of trainee doctors. The evidence for an association between sleep deprivation and doctor performance is not as plain as logic suggests, although many authors point out that there are limitations to their studies. For instance, measurement of performance is often based on completion of a single task done after a call shift. These studies fail to take into account the effects of chronic fatigue on overall patient safety. Future studies that follow patient outcomes over extended periods of time and include a range of procedures may be beneficial. Even if there is no clear case for a detrimental effect on patient health, sleep deprivation certainly affects the physical and mental well being of doctors. Most studies lack insight into a lifetime of sleep deprivation and stress. Current strategies to mitigate this issue have focused on reducing work hours. However, this may only serve to decrease the amount of time allotted to do the same amount of work. Future research should focus on developing more strategies, such as night float, which reduce work compression, and on ways to better utilise and train doctors in a shorter period of time. Based on the evidence to date, a great deal more work is required in this field to better serve patients and doctors alike.

References
Unplugging platelet function tests: reassessing the gold standard

Abstract
As students of medicine and the allied healthcare fields, we are taught to assess research methodology with a critical eye and not to take conclusions at face value. How often, however, are we encouraged to question established practice? This article describes the re-evaluation of current best practice in diagnosing platelet function abnormalities. The gold standard test among platelet function tests (PFTs) is light transmission aggregometry (LTA). This test has been used for more than two decades, and it has only recently been proposed that LTA is due for re-evaluation; critics suggest that it never wholly fulfilled its function to begin with.

Introduction
The concept of platelets existing in blood was discovered more than 120 years ago. The use of tests to assess their function began in 1910 at Duke University, when researchers postulated that bleeding time provided an indirect measure of platelet function. The Duke bleeding time test is simple: the skin is punctured using a needle and the length of time taken for bleeding to stop is measured.\(^1\) Since then other tests have been developed which use newer technology to measure platelet function. Light transmission aggregometry (LTA) was developed in the 1960s and has since been considered the gold standard method for measuring platelet function.\(^2\) No new tests have been introduced since LTA, and only recently have critics begun to suggest that it may never have wholly fulfilled its function.

Biomedical research is continually reshaping the way medicine and the allied healthcare fields are understood and practised. The way we do research has evolved dramatically over the last century; from individually conducted investigations subjected to no regulatory bodies, what we understand as ‘research’ is a field integral to scientific progress, requiring teamwork, accuracy, and reproducible methods, with strict adherence to an ethical code. The volume of research we produce has also escalated to numbers that could not have seemed possible even decades ago. MEDLINE, an online database of published biomedical research, has added anywhere from 500,000 to nearly 900,000 new citations every year.
Platelet function tests
The value of being able to accurately assess platelet function is unquestionable. Still, there has been little interest in developing new and better methods for doing so. Though the newest test is at least 20 years old and the others even older, only recently has their primary function been questioned.

Bleeding time
Researchers at Duke University first introduced the concept of measuring platelet function by the length of time it took for bleeding to stop following a pinprick. Bleeding time testing was easy, cheap, and could be done at the bedside. Though newer tests were later developed, bleeding time continued to be used until the early 1990s. After this time clinicians began to abandon bleeding time in favour of less invasive and time-consuming tests. Even so, it was and still is one of very few tests that measures platelet function in vivo.

Light transmission aggregometry
In LTA, a sample of blood is taken and an agonist introduced, then the sample is stirred to initiate coagulation. This process mimics the intravascular stress that platelets are subjected to in the event of an endothelial injury. Platelets in the blood sample are activated and clump together, and the clumps fall to the bottom of the test tube causing the sample to clear. Light is then passed through the tube by an aggregometer.

Platelets play a major role in the tight regulation of homeostasis in our blood. Normally our blood vessels are lined with a protective layer of endothelial cells, which guards the underlying connective tissue from exposure to blood. However, if there is a break or intravascular injury to the endothelial lining, collagen (a potent activator of platelets) is exposed to the intravascular blood and initiation of coagulation commences. Resting platelets circulate as discoid cells, however, when they encounter extravascular material such as collagen, their morphology changes and they become activated, assisting in the formation of a ‘homeostatic plug’. This plug, which consists mostly of platelets, walls off the area of injury until a fully formed thrombus can seal it off. If this thrombus occludes a vessel that supplies heart muscle, or breaks off and travels into the brain, serious damage may occur to the tissue.

Measurement of platelets is crucial for assessing thrombotic risk. It also provides important information for determining post-intervention risk of thrombosis. For example, PFTs may give an indication of the risk of developing a major adverse cardiac event (MACE) after a percutaneous coronary intervention (PCI). They also help in assessing preoperative bleeding status and bleeding risk during surgical procedures.
Do PFTs tell us what we really want to know?

The ideal characteristics of a PFT for screening and diagnosis can be summarised in four points.1 A PFT should be able to:

1. Detect platelet hyper-reactivity at baseline.
2. Detect inter-patient variation in platelet reactivity to allow individualised antiplatelet medication.
4. Predict bleeding risk.

To date there is no test that fits the above criteria, including LTA. Current PFTs do not give a clear definition of a normal and a hyper-reactive range.10 They are also not ideal for individualising antiplatelet therapy. Petricevic et al. point out that even when giving antiplatelet therapy, the expected platelet inhibition does not always happen – in fact up to 45% of patients have a low response to aspirin or clopidogrel.11 PFTs do not reliably measure response to antiplatelet therapy, nor do they detect resistance to therapy. They cannot differentiate between patients who are on or off clopidogrel, making it very difficult to diagnose compliance with antiplatelet medication regimens.12 Current PFTs also do not definitively measure the risk of future thrombosis or bleeding. In one study, the PFA-100 did not predict the risk of MACE after PCI or stent thrombosis following a drug-eluting stent (DES) implantation.10,13 PFTs also do not always reflect bleeding risk. Assessing bleeding risk is crucial prior to surgical procedures; this affects the time at which preoperative antiplatelet management is stopped and postoperative bleeding risk assessed.11 If PFTs cannot accurately predict these risks, clinical decisions cannot be made based on their results.

The need to re-evaluate established practice

In light of this evidence, maybe it is time to assess the value of current PFTs on a larger scale. Although most of these tests have been in use for decades, only recently has the observation been made that they are not fulfilling their purpose.10 Until this is done, current PFTs will continue to be used in clinical practice and remain the gold standard. We take for granted that the evidence-based practices in use are built on the best evidence available, however, this is not always the case. Despite the great quantity of scientific research that is generated every year, it is important to be mindful of the quality of this research and whether it is appropriately integrated into day-to-day practice. Published results take time to be implemented, and only research that makes it to publication can inform whether we change our practice; negative and unpublished results are much more difficult to incorporate. These considerations are important for us as students in the healthcare field. Our attitudes towards accepting current best practice as students will form the attitudes we have as professionals. PFTs are only one example of the kind of practices that we should be questioning as we move forward in our careers. With this example in mind, we must continue our studies as future healthcare practitioners who are not only receptive but also thoughtful and analytical.

References

Sources of, and barriers to, healthcare in armed conflicts

Abstract
Armed conflict challenges healthcare providers by creating new threats to health and limiting healthcare resources. This article looks at some of the major armed conflicts of the 20th and 21st centuries, and examines the specific threats posed to the health of populations affected, using the conflicts in Rwanda, the Western Balkans and Syria as specific case examples. Sources of healthcare resources are critiqued, and the relative advantages and disadvantages of humanitarian intervention versus humanitarian assistance are explored. The vulnerabilities and limitations of humanitarian assistance are identified, with special attention to examples from recent armed conflicts. Finally, this article discusses the challenges facing the international community in making collaborative decisions about the best providers of healthcare in armed conflict. These challenges include many competing interests and limitations of the United Nations as a primary body for making decisions regarding the legitimacy of humanitarian intervention.

Introduction
“The only thing necessary for the triumph of evil is that good men should do nothing.”

This is a quote often attributed, rightly or wrongly, to Irish political philosopher and statesman Edmund Burke. Whatever the true source of this quote, it is an aphorism that often appears whenever the issue of humanitarian intervention during times of armed conflict is raised. At the end of the 20th century, the Rwandan genocide and Balkans war challenged global notions of responsibility to intervene. Both involved international intervention, which was widely considered to have been mishandled. The 21st century has given us its own challenges, with the United States-led invasion of Iraq garnering much international criticism for its lack of a United Nations (UN) mandate, and accusations of the US using the pretence of humanitarian
intervention to further its own geopolitical interests. In recent times the intervention *debat du jour* is whether Western nations should intervene in Syria on humanitarian grounds in response to the use of chemical weapons on civilians by the Assad regime. This article examines humanitarian assistance and intervention from a health perspective in the context of armed conflict. The types of humanitarian assistance – both military and non-military – are discussed, and the benefits and pitfalls of each for the health of populations are explored.

**Humanitarian assistance versus humanitarian intervention**
Whereas humanitarian assistance refers to non-military organisations providing aid to people affected by humanitarian crises and is protected by international humanitarian law, there is much debate among academics as to what constitutes humanitarian intervention, with no international consensus. One definition is: “humanitarian coercive action by states involving the use of armed force in another state without the consent of its government, with or without authorisation from the United Nations Security Council, for the purpose of preventing or putting to a halt gross and massive violations of human rights or international humanitarian law”. This lack of consensus is not merely academic, but extends to multilateral organisations such as the UN and the North Atlantic Treaty Organisation (NATO). As there is no international consensus on what humanitarian intervention entails, problems arise when an intervention purported by a state to be undertaken on humanitarian grounds is opposed by the international community, as was the experience when the US declared war on Iraq in 2003, in the absence of a UN mandate.

**The need for humanitarian assistance**
Armed conflicts have a profound effect on the general health of nations. Not only do particular healthcare needs increase as a direct result of armed conflicts (Table 1), but when states are engaged in armed conflict, spending may be diverted from healthcare to fund the conflict. This mismatch between healthcare supply and demand creates a long-lasting dependency on external aid.

In addition, in times of armed conflict these increased healthcare needs may be provided for by local political or paramilitary organisations that use the provision of badly-needed healthcare and education to garner political capital. They then redeems this for positions of political authority, as is the case with Hezbollah in Lebanon and Palestine. In addition to the relief of suffering during armed conflict, public health activities promote peace, prevent violence and allow enemies to reconcile.

**Humanitarian organisations**
Apolitical humanitarian organisations such as Médecins Sans Frontières (MSF), the UN and the International Red Cross/Crescent represent an alternative to political organisations in areas of armed conflict. These organisations allocate health resources to the people affected by armed conflict on the basis of need and not political affiliation, allowing them to operate in conflict zones tolerated by the conflicting parties. A further advantage of these groups is that their intervention is based on humanitarian grounds and not the promise of gaining a geopolitical advantage, as may be seen when states or blocks of states intervene in armed conflicts under ostensibly ‘humanitarian’ grounds. The International Committee of the Red Cross/Crescent (ICRC) is particularly well placed to serve the needs of people affected by complex humanitarian emergencies, as it has local branches in almost every zone of conflict and can ultimately allow local healthcare workers to assume responsibility for primary healthcare, thus decreasing dependence on external intervention.
Vulnerability
Humanitarian workers, including both military and non-military medical personnel, are protected from attack under the Geneva Convention and its additional protocols. The convention declares that medical personnel should be afforded specific protection from attacks and that they should not be prevented or prohibited from providing medical care to those who need it. However, in reality the disadvantage of humanitarian organisations is that their apolitical, non-military stance makes their workers vulnerable, as they have little means to protect themselves in the face of aggression. While the concept of international law protecting medical personnel may seem noble, those engaged in armed conflict tend to care little for compliance with such laws; the mere existence of the International Criminal Court (ICC) is testament to this fact. Attack on medical vehicles branded with Red Cross and Red Crescent signage in Afghanistan, coupled with the 2009 kidnapping of Irish aid worker Sharon Commins and her Ugandan colleague Hilda Kawuki in Darfur in Sudan, serve as sober reminders of the vulnerability of humanitarian workers in apolitical, non-military organisations.

Military intervention
A third provider of healthcare in regions of armed conflict is individual states or blocks of states, such as NATO or the UN. They have the advantage of being militarily equipped and thus able to defend themselves and their equipment, as well as their medical corps having the protection of international law under the Geneva Convention. However, the invasion of one nation state by another directly contravenes the sovereignty of the invaded state, regardless of the grounds for invasion. Thus, medical and military personnel from the invading state are at increased risk of violence and aggression as the invaded state attempts to defend itself. The individual medical corps of NATO forces were only able to provide limited healthcare to Kosovan refugees in Stenkovec One refugee camp in Macedonia during the war in the Western Balkans in 1999; as they were active combatants in a war, their presence endangered the lives of the refugees.

A further hazard of military humanitarian intervention is that, while apolitical humanitarian organisations direct their aid towards those regions that require it most, military intervention is strongly influenced by strategic regional interests and international relations. UN peacekeeping troops have the advantage of being non-aggressors and favouring no particular side during a conflict; their stated role is purely to preserve peace. But even their presence did not prevent the genocide of Rwandan Tutsis by Hutu gangs in 1994.

Conclusion
Humanitarian aid and intervention is fraught with difficult ethical decisions – to close the medical centre and put patients at risk, or to force staff to work in an environment with a high probability of rape? To provide healthcare by an army corps in the knowledge that its presence may draw fire on a refugee camp? To violate the sovereignty of another country to ‘save’ its people from its leader? The ‘right’ answers to these questions often only become apparent retrospectively after much discussion and analysis, but may still be a subject of debate for generations. When considering the superiority of one form of health service delivery over another, it is important to examine the evidence at hand. NGOs offering humanitarian assistance must be
undertakes health initiatives around the world through the multilateral organisation in the world is the UN, which influence over the area for geopolitical advantage. The largest possible – to avoid a dominant military force exerting undue influence, the decision to intervene should be taken multilaterally – in so far as it is augment the work of non-military organisations, the decision to intervene should be maximised in complex humanitarian emergencies in order to minimise the effect of armed conflict on the health of populations.

In cases where there is a tangible threat to the provision of humanitarian assistance by conflicting armed forces, it is then legitimate for an external military party to intervene, provided that the intention of the intervention is to preserve the integrity of such relief efforts and not to further strategic regional interests.

In these cases, where military intervention is needed to augment the work of non-military organisations, the decision to intervene should be taken multilaterally – in so far as it is possible – to avoid a dominant military force exerting undue influence over the area for geopolitical advantage. The largest multilateral organisation in the world is the UN, which undertakes health initiatives around the world through the World Health Organisation (WHO). The UN subscribes to the idea of ‘responsibility to protect’, believing that: “The international community has a responsibility to use appropriate diplomatic, humanitarian and other means to protect populations... If a state is manifestly failing to protect its populations, the international community must be prepared to take collective action to protect populations, in accordance with the UN Charter”. However, when it comes to issues of humanitarian intervention, the vetoing power of the United States, China, Russia, the United Kingdom and France within the United Nations’ Security Council can act as a barrier to intervention.

This barrier may not necessarily be a disadvantage, as it may act to prevent one dominant power exerting undue influence, but equally it can prevent timely humanitarian assistance from reaching vulnerable populations. There is no easy answer as to when humanitarian intervention may be used; indeed, the UN itself does not have a set of criteria for when it will intervene, preferring instead to judge each conflict on its individual situation.

As armed conflict increases in the Middle East and Africa, it is likely that humanitarian organisations will become increasingly limited in what they can provide, as is already the case in Syria, with five staff members of MSF having been detained in January of this year. This will increase the need for humanitarian intervention to bring stability to conflict zones so that NGOs can continue to provide healthcare to populations affected by violence.

References

Whose life, whose death?: Pharmaceutical trials in the developing world

Amelia Reid
RCSI medical student

Introduction

In Kano, a small Nigerian town on the southern edge of the Sahara desert, approximately 5,000 children will die of bacterial meningitis during the dry season in any given year. The entrenched poverty and arid, unsanitary conditions are ideal for the spread of infectious diseases such as measles, cholera and bacterial meningitis. During the worst dry season on record – 1996 – an epidemic swept through Kano and killed more than 11,000 children. Médecins Sans Frontières health personnel were providing treatment to those families who could not otherwise afford it, or were unable to be seen at the already overflowing government hospital. At the time, the World Health Organisation (WHO) recommended that the first line of treatment for children who presented with suspected bacterial meningitis should be chloramphenicol – a cheap,
prototypical, broad-spectrum antibiotic. Midway through this epidemic, a team from Pfizer flew to Kano from the United States to recruit subjects for a trial of trovafloxacin (Trovan), its new orally delivered antibiotic. Trovan, a quinolone antibiotic, was yet to be proven effective against bacterial meningitis. The safety of Trovan had not been established and initial animal studies had not yielded promising results. In fact, Pfizer would later be advised by the Food and Drug Administration (FDA) to remove Trovan from the market because of concerns about liver toxicity.

In the United States, where Pfizer has its headquarters, approximately 4,000 people contract bacterial meningitis every year. However, in Nigeria, Pfizer could recruit hundreds, if not thousands of paediatric patients with the illness in a matter of weeks. If they were able to establish that Trovan was effective for the treatment of meningitis in children, Pfizer would break into the lucrative worldwide paediatric market, including countries where there is either a high incidence of the disease or periodic epidemics.

The Trovan study presents a myriad of ethical quandaries. Is the use of a trial drug or treatment, where no other choice exists, a form of coercion? Is it ethical to run a trial of expensive new drugs in a country where that particular medication will, in all likelihood, never be affordable for most people? Is it acceptable to conduct a trial on subjects without their explicit and informed consent, even if the researchers are reasonably certain the drug is better than the current ‘gold standard’?

Coercion

The conduct of clinical trials in developing countries by researchers from the developed world has become more commonplace over the last three decades. Apart from the relative ease of recruiting subjects, companies can make significant savings on human labour, which accounts for around half of the costs incurred. In India, an academic institution or affiliated hospital is said to charge approximately 10 times less for recruiting participants and conducting a preliminary trial than centres in the United States. Furthermore, there are fewer regulatory obstacles for researchers to overcome in developing countries, and this presents another significant incentive. Some might argue that the high front-end costs of developing a new drug justify the most cost-efficient methods of testing its efficacy.

The incentives to lower costs are patent: it is estimated that the cost of manufacturing one new drug can be in excess of US$5 billion. A pharmaceutical executive wrote that, between 2000 and 2008, the price of shares in the top 15 pharmaceutical companies dropped by more than half – from 32 to 13 times earnings. Pharmaceutical companies are, in a perverse sense, aided and abetted in their efforts by the very people they seek to recruit. For the very poor who cannot afford healthcare, or are living in areas where access to health infrastructure or personnel is limited, a clinical trial is a way of obtaining free treatment or care. Most trials involve clinical testing, medication, and follow-up free of charge – all of which would be otherwise inaccessible. Moreover, the apparent authority and status of the providers gives those without the knowledge or means to judge the reassurance that their treatment is effective and safe. Coercion is not synonymous with an explicit threat; the threat is inherent in the transaction. If the subjects do not accept what they are offered, they may well be offered nothing – an unpalatable choice when one’s child is ill or near death.

Access

Until 2008, the FDA required that all trials conducted in foreign countries comply with the Declaration of Helsinki. However, this is no longer the case. Foreign trials are now only required to comply with “good clinical practice guidelines” (GCP). These guidelines, outlined by the International Conference on Harmonisation – a group aimed at bringing together authorities from the regulatory bodies in Japan, the USA and Europe – are worthy, but do not encompass all of the principles outlined in the Declaration of Helsinki. For instance, one of the tenets of the Declaration is that...
drug testing can only be conducted on a population that will, in all probability, be afforded access to and benefit from those drugs in the long term. The GCP guidelines do not require this.\textsuperscript{1,10}

In impoverished countries, as in the case of the disenfranchised poor in the West, access to even basic healthcare is marginal at best. Variables such as income, education, employment, geography, and culture influence life’s chances across a spectrum of health conditions and have well-demonstrated impacts on longevity. In this context, one of the weighty dilemmas facing researchers is whether to conduct a trial for a new therapy against the best available treatment anywhere in the world or the best available treatment in that country.\textsuperscript{10,11} Some have defended the use of placebo-controlled studies on the grounds that the controls are receiving no more and no less than they would normally receive (little or nothing), and those receiving the experimental drug may benefit.\textsuperscript{11} In a developed country, ‘standard of care’ is taken to mean the best evidence-based practice, not a standard determined by the relative wealth or poverty of the study population.\textsuperscript{9,10} The ‘better than nothing’ defence has a certain seductive logic, but it scarcely meets the criterion of moral defensibility.

For instance, the AIDS Clinical Trial Group (ACTG) Study 076, which compared vertical transmission rates of HIV in pregnant women receiving the antiretroviral drug zidovudine versus placebo, was prematurely stopped when it became clear that those receiving zidovudine had much lower transmission rates.\textsuperscript{12} Zidovudine soon became the standard of care in the United States. However, the regime is unaffordable for most people in countries where the maternal-foetal transmission of HIV is at epidemic proportions.\textsuperscript{13,14} In Uganda, to administer the zidovudine regimen to HIV-infected pregnant women would cost 400 times the country’s yearly expenditure on healthcare.\textsuperscript{15} A less costly alternative was therefore urgently needed. WHO officials concluded that placebo-controlled trials would ‘offer the best option for obtaining rapid results’.\textsuperscript{16} Subsequently, 18 placebo-controlled trials, involving more than 17,000 women, were undertaken in several developing countries, which aimed to assess a number of interventions to reduce mother-to-child HIV transmission rates. These included the use of vitamin A and intrapartum vaginal washing.\textsuperscript{14} The ‘better than nothing’ principle was thus brought to bear on a crisis by those whose only interest was in arresting the epidemic. For ‘big pharma’, the conflicts of interest are acute and the risk of exploitation real, most especially if the drugs being tested will never be accessible to those whose bodies were used to establish their efficacy.

**Informed consent**

The first clause of the Nuremberg Code – developed after the Second World War and to which researchers must conform when undertaking studies on humans – holds that subjects of research should give informed and voluntary consent, and be able to exercise the ‘free power of choice’, including the right to opt out of a trial at any stage.\textsuperscript{17,18} The Declaration of Helsinki, adopted in 1964, holds that subjects in a trial must fully understand the anticipated benefits and risks and be aware of any conflicts of interest the researchers involved might have.\textsuperscript{19,20} These documents established the principle of informed consent for participants in research. Unfortunately, many study participants from the developing world are unaware of their rights or the obligations of researchers, and do not understand the risks when they enroll in a trial.\textsuperscript{21} The problem in Kano was this: the ethical regulations that guide research and trials in any developed country are not applied with the same rigour and oversight in the developing world. Pfizer did not have to gain the approval of the FDA prior to leaving for Kano.\textsuperscript{22} They argued that there was no international protocol or accepted norm requiring them to obtain informed consent when undertaking research with experimental drugs in Africa.\textsuperscript{4} The participants in the trial were not asked to sign consent forms prior to being assigned to an arm of the trial. Pfizer alleged that the children were too young to sign and the parents did not speak enough English to understand the purposes and risks of the trial, and therefore, to give informed consent. The parents later claimed that they did not even know their children were part of a clinical trial.\textsuperscript{4} Obtaining truly informed consent from a vulnerable individual or population in a culturally appropriate way and with research integrity may be difficult, but this does not release researchers from the obligation.\textsuperscript{23} The standard consent procedures utilised in developed countries are not necessarily appropriate in settings where there are language and social barriers, a lack of individual autonomy (for instance, in conservative patriarchal societies) or hesitation by the participants to challenge authority. In Kenya, researchers who wanted to conduct a trial on orphaned children were required to adhere to the sociocultural norms of the ‘Mabaraza’ – a traditional hierarchical community assembly. The benefits were twofold; the researchers were better able to understand the
community perspectives and beliefs on health and healthcare delivery; and, the local community were more amenable to the researchers and their work as they felt their values and traditions had been considered and respected.24,25

Conclusion
In 2007, the Nigerian government sought to sue Pfizer for US$7 billion. The final outcome of the case – a reported US$75 million settlement – is subject to a confidentiality agreement.30 However, some of the more embarrassing and damning details were leaked through the Wikileaks cables, prompting Pfizer to issue several justificatory press releases.26 The Nigerian Health Ministry has since released a report on the trial saying that Pfizer violated Nigerian law, the UN Declaration on the Rights of the Child and the Declaration of Helsinki.27

While unregulated clinical trials are conducted in poor countries, we in the West are conflicted, knowing that our medical care may come at the cost of others’ well-being and of the moral integrity of our corporations. The question, then, is whether we in the developed nations insist on the same enforceable standards for others, who do not have the same voice or means, even if that means foregoing, or slowing, the availability of new and more effective drugs. It is not just a matter of life and death, but whose life, and whose death.

References
Ensuring safe surgery for our patients – DO WE DO ENOUGH?

DAVID HAKIM looks at attitudes to surgical safety, particularly in the UK health service.

Last year in the UK, 223 people died while undergoing surgical procedures. Statistics produced by the UK’s National Health Service (NHS) show that 28.3% of all operations carried out last year were associated with some form of complication – defined as any undesirable or unexpected result.\(^1\)\(^2\) Although only 0.1% of these were fatal, complications still carry a high potential for morbidity.\(^2\)

Post-surgical infections, for example, range from mild cellulitis to uncontrollable sepsis with variable morbidity.\(^3\) When standard preoperative, intraoperative, and postoperative safety measures are taken, infections still sometimes occur.\(^4\)

In 2001, the US National Quality Forum (NQF) introduced the concept of the ‘never event’ and defined 27 surgical events, including wrong site, wrong patient and wrong procedure, which should never occur.\(^5\) Medical and surgical advances over the last decade have undeniably made today’s healthcare system safer and much more efficient than it was when the initial list was released. Despite this, the ‘never event’ tally is still worryingly high, which forces us to ask: are we doing enough?

The checklist manifesto

One successful strategy, endorsed by the World Health Organisation (WHO), is the ‘time out’ surgical safety checklist, which was developed in partnership with Harvard-based general surgeon, author, and pioneer in error reduction, Atul Gawande. Since its 2007 introduction, the checklist has been applied by more than 4,000 hospitals in 122 countries. The UK Department of Health successfully implemented this checklist across all hospitals by February 2010. Publications from several medical centres – such as the 2009 Gawande et al. pilot study of eight hospitals worldwide\(^6\) – continue to confirm that use of the WHO checklist improves communication and increases the reliability of “routine interventions such as antibiotic prophylaxis and thromboembolic prophylaxis”.\(^7\)

Gawande was inspired to create surgical checklists after watching pilots perform pre-flight checks before every take-off.\(^8\) He continues to lead the Safe Surgery Saves Lives (SSSL) initiative of the patient safety division at the WHO.\(^9\) Studies done by SSSL...
found that there were improvements in safety attitudes, which positively correlated with the reduction of postoperative complication rates. In total, 93.4% of clinicians questioned by the SSSL stated that before having an operation, they would want the checklist to be used.\textsuperscript{10}

There are, however, those who remain critical of this safety precaution. According to the President of the Royal College of Anaesthetists, 37% of medics are against the scheme; they find that there is insufficient time to use the checklist in operating theatres.\textsuperscript{11}

\textbf{Use of the WHO checklist improves communication and increases the reliability of “routine interventions such as antibiotic prophylaxis and thromboembolic prophylaxis”.\textsuperscript{7}}

\textbf{Communication}

Another important contributor to safe surgery is the level of communication in the operating theatre. Communication failures are a well-known cause of inadvertent patient harm across medical specialties.\textsuperscript{12} Over the last decade or so, team performance has been identified as an essential foundation of good surgical care; open channels of communication within a team are a key determinant of how well the team functions.\textsuperscript{13} This presents a special challenge in the field of surgery, which is traditionally rigidly hierarchical.\textsuperscript{14}

Promotion of an open atmosphere, wherein less senior team members are comfortable bringing potential problems to the attention of their superiors, is especially important, as teamwork and communication have been shown to be correlated with better surgical outcomes.\textsuperscript{15,16}

In medical centres with internationally trained staff, language presents another potential barrier to communication.\textsuperscript{17} The UK’s Medical Act of 1983 prevents the General Medical Council (GMC) from doing any language testing of doctors from the European Economic Area (EEA). However, the GMC and the Nursing and Midwifery Council argue that failing to test foreign medics’ English exposes patients to serious risks.\textsuperscript{18} Asking that operating theatre staff be expected to speak English to a certain standard, therefore, is not an unreasonable request. The 30-year-old Medical Act needs re-evaluation to address this issue.

\textbf{Technology}

Surgery has evolved dramatically in the past two decades.\textsuperscript{19} The first minimally invasive procedure – a laparoscopic cholecystectomy – was performed in 1987.\textsuperscript{20} Since then the field has burgeoned; minimally invasive options for complex procedures such as cardiac valve replacement and donor nephrectomies exist.\textsuperscript{21,22} Minimally invasive surgery (MIS) offers benefits such as: shorter operation times; smaller incisions; reduced postoperative trauma; and, smaller amounts of blood loss.\textsuperscript{23} For example, the ‘finger-assisted nephrectomy’ technique allows significantly smaller incision lengths than the traditional open procedure, without risking patient safety and with fewer postoperative complications.\textsuperscript{24} This is not only beneficial to the patient but to the hospital and doctors too; quicker operations and shorter hospitalisation times allow more patients to be treated. MIS procedures use video-assisted equipment, allowing the surgeon better visualisation and magnification of internal organs and structure. This translates into a more accurate and definitive procedure for patients.\textsuperscript{25} Today’s surgeons should
familiarise themselves with these techniques in order to raise the standard of patient safety.

Robotic surgery is another area being tested and implemented in some institutions. This provides several advantages, including the minimisation of human error, which should correlate with increased accuracy and precision. However, the associated cost and increased operation lengths are disadvantages. Nevertheless, if investment in robotic technology means a significant reduction in surgical error, then it is definitely worth developing.

Over the past decade, surgical instruments – including staplers, scalpels and endoscopes – have also been redesigned to reduce surgical complications. The use of HemoStase™, a powdered polysaccharide haemostat, is an example of new technology used to control bleeding during surgical procedures. During 2009-2010, a study was done at the West London Renal and Transplant Centre (Imperial College Healthcare) to demonstrate the benefits of HemoStase™; 44 consecutive patients who underwent live donor nephrectomies had a 100% haemostasis success rate when the powder was administered. None experienced postoperative bleeding, fluid collection or infection, or required re-exploration of the surgical site. Unfortunately, the NHS has been hesitant to invest in equipment that has been adopted in the private sector. For example, some NHS hospitals do not use the harmonic scalpel. This instrument both cuts and coagulates tissue instantaneously; instead, NHS hospitals use traditional methods such as electrocautery. Another example is the Cook-Swartz doppler flow monitoring system – a 1.0mm Doppler probe attached to a cuff of expanded polytetrafluoroethylene (GORE-TEX; WL Gore and Associates, Flagstaff, Arizona), which is secured around a vessel and sutured in place providing real-time monitoring of blood flow – used to analyse organ viability after procedures such as kidney transplants. The prohibitive cost of this technology means that in NHS hospitals, traditional ultrasound is still being used.

Conclusion

Unfortunately, the truth is that we are falling short of our patients’ safety expectations. 2011-2012 saw thousands of surgical incidents reported to the UK’s National Patient Safety Agency: 161 patients left operating theatres with surgical instruments still inside them; 41 patients had the wrong implant or prosthetic inserted; and, 10 people had incompatible blood transfused during operations. These figures emphasise the need for action against risk. Associations such as the UK’s Patient First, the stated purpose of which is to “reduce death and harm in the NHS and to force the UK Government to create policies and laws that ensure the NHS becomes open and accountable” continue to support and promote the goal of surgical safety, reminding us that patient safety is always the top priority. ‘Never events’ should at no time be tolerated and are eminently preventable in the NHS. This is a global issue, demanding the authority of the WHO, which has produced schemes to try and reduce surgical risks. We sadly cannot say that we have done enough to reduce surgical complications; however, the initiatives taken in recent years have proven to be effective. With further work and determination our doctors and future doctors can and will reduce the risks involved with surgery. Hippocrates stated 2,500 years ago, “… a great doctor has the value and strength of many other people together…” This is something that must be proven right. The only way to do this is to continue to reduce the risks involved in this life-saving occupation.

According to the President of the Royal College of Anaesthetists, 37% of medics are against using checklists; they find that there is insufficient time in operating theatres.
References


The white coat: 
DOES IT HAVE A FUTURE IN IRELAND?

EOIN KELLEHER explores the future of the white coat in Irish hospitals, and what a doctor should wear.

Introduction
The white coat and stethoscope are the most recognisable symbols of our profession. The white coat rose to popularity among surgeons because of its association with groundbreaking scientific achievements that characterised the 19th century.\(^1\) It came to be associated with science, cleanliness and professionalism. It maintained its popularity among the profession through tradition; symbols and traditions are important in all cultures, medicine being no different. 'White coat ceremonies' have become a rite of passage in modern medical schools. The first was held in Columbia University, New York\(^2,3\) in 1993, and spread to Ireland, with the Royal College of Surgeons in Ireland (RCSI) holding the first such ceremony (Figure 1). They are now a part of the culture in many medical schools on the island and elsewhere.
A consequence of the 2007 UK law – and changing worldwide fashions – has been a lively debate in the profession about what a doctor should wear. Many patients complain that they cannot identify who in the hospital is a doctor, and among doctors they cannot tell what their rank is.

The white coat falls out of favour
In recent years, however, the white coat has fallen out of fashion in hospitals. It began with paediatrics and psychiatry, which eliminated the use of the white coat because it was felt it presented a barrier to the doctor-patient relationship. Public health doctors and pathologists soon followed. Physicians themselves gradually dropped the garment, and now even many surgeons do not wear them. In 2007, the UK Government instituted a ‘bare below the elbows’ (BBE) policy across the National Health Service (NHS), which effectively sounded the death knell for the white coat, which joined neckties and cuffs in the realm of obsolescence in the UK.

Even in most Irish hospitals you would be hard pressed to find even one qualified doctor who regularly wears a white coat. In fact, medical students are the one remaining group who wear the white coat regularly. However, this is also going out of fashion, with many hospitals in Ireland banning the white coat from their wards, notably the children’s hospitals.

What should a doctor wear?
A consequence of the 2007 UK law – and changing worldwide fashions – has been a lively debate in the profession about what a doctor should wear. Many patients complain that they cannot identify who in the hospital is a doctor, and among doctors they cannot tell what their rank is. With many medical students no longer wearing white coats, this adds to the confusion.

In addition, the casual clothing that has replaced coats, particularly in UK hospitals, has given rise to complaints about a lack of professionalism.

A symbol of elitism
However, many are happy to see the white coat go. To some, it symbolises the elitism and privilege associated with stereotypes of doctors. They fear doctors ‘become the coat’ and fail to empathise with their patient as a fellow human being. The white coat, it is argued, represents a hierarchy of care that places the consultant physician at the pinnacle and everyone else beneath them. It is partially for these reasons that paediatricians and psychiatrists long ago lost the coat. The length and weight of a white coat used to be a marker of seniority. An interesting study from Edinburgh demonstrated an inverse correlation between the mean weights of white coats and physicians’ seniority. A junior house officer had 1.7kg weighing him down on average, compared to 1kg for a consultant.

Bare below the elbows
Along less philosophical lines, many argue that the white coat should be abandoned because it is unhygienic. Studies have shown white coats to harbour pathogens, and that long sleeves may transmit these to patients. In addition, since most hospitals in the UK and Ireland have stopped providing laundry services for workers’ uniforms, white coats are not being washed as frequently.
A study of London medical students (prior to the BBE policy) found that the vast majority only washed their coats occasionally, and that the sleeves and pockets were contaminated with organisms such as *Staphylococcus aureus*.\(^5\)

White coats, in addition to neckties, lanyards, watches and long sleeves, it is argued, should be discarded. However, the evidence to support changing clothing policy for hygiene reasons is scanty.

A review on the topic, commissioned by the Department of Health in the UK, stated that: “Although it has been hypothesised that contaminated uniforms are a potential vehicle for the transmission of pathogens, no studies demonstrated the transfer of micro-organisms from uniforms to patients in the clinical situation”.\(^15\)

Indeed, it has not been reliably demonstrated that the white coat, or indeed any item of clothing, contributes to hospital-acquired infections.\(^14\) The impact of the BBE policy in the UK has also been mixed. One argument in its favour is that, even if shirtsleeves themselves do not cause transmission of hospital-acquired infections, having bare arms and wrists promotes better hand hygiene. However, this has not been borne out by evidence, with one study showing no difference in hand hygiene between doctors who followed the BBE policy and those who did not.\(^16\)

In the UK, many argue that the BBE policy was introduced as a public relations exercise to demonstrate that action was being taken against ‘hospital superbugs’, which were being portrayed in the media. It is easy and cheap to issue clothing policies, while it is more difficult to tackle more fundamental causes of hospital-acquired infections, such as patient overcrowding and antibiotic misuse.\(^17\)

On balance, it seems prudent to regard long-sleeved white coats as reservoirs of pathogens, particularly when they reside solely on medical students who are in frequent close contact with patients, have yet to develop a strong sense of hand hygiene, and who are not given to regularly washing their coats.\(^5\)

**Does it matter what a doctor wears?**

Doctors are one of the few groups in healthcare who do not wear uniforms. With more and more hospitals discarding the white coat, one can ask, does it really matter what a doctor wears? The answer, it seems, is yes (Figure 2).

There are many studies that demonstrate that patients prefer their doctors to look professional.\(^6\) Many show that patients prefer doctors to wear white coats, while many are equivocal. A study by Au *et al.*\(^18\) asked family members of ICU patients to complete a questionnaire rating the importance of different aspects of doctors’ appearance.

They then asked them to select the best physician from a panel of four photographs, which depicted doctors in clothing that ranged from jeans to a business suit, a white coat, and scrubs. Unsurprisingly, jeans fared worst, with only 10% favouring them. Surprisingly, the business suit (commonly worn by many doctors in Ireland), fared next worst, being preferred by only 12%. The white coat was the overall favourite, being favoured by over half of family members, with scrubs being favoured by one-quarter. What is interesting is that the white coat and scrubs are both the most specific garments associated with doctors, and both were most associated with being ‘caring’ and ‘competent’. Other studies have shown similar results, with garments specific to doctors, such as the white coat and scrubs, being preferred.\(^7,19,20\)

Why might this be the case? First, these items of clothing clearly identify the person as a doctor, which carries with it associations of competency, caring and professionalism. These create a vital good first impression with a patient. First impressions are important in medicine because most clinical encounters are very brief. With most consultations lasting a matter of minutes, it is vital to establish a good rapport.

Additionally, it can be difficult for a patient to identify who is a doctor, and among doctors to identify who is a student, who is the intern and who is their consultant, particularly if everyone is wearing his or her own clothes.

ID badges are often cited as an answer to this, but the vast majority of patients report that ID badges are not visible, or that the writing is too small.\(^7\) Additionally, lanyards – much like neckties – are a source of infection and so are not ideal for advertising one’s rank.\(^12\)

**A uniform for doctors?**

So far we have identified several themes. The white coat, which was once the brand image of the medical profession, is disappearing; it is now effectively extinct among doctors and is in decline among medical students.

Patients want their doctors to look professional, and prefer items of clothing specific to healthcare, rather than business suits. Indeed, new infection control measures mean that neckties and long shirtsleeves are also not likely to be a feature of Irish hospitals much longer, much like the UK. However, these same infection control measures mean that the traditional long-sleeved, billowing white coat is unlikely to stage a comeback. So what are medics to wear?

Perhaps it is time to consider uniforms for doctors in Irish hospitals. These would have a number of advantages. First, and most importantly, it would mean that all grades, from student to consultant, are easily identifiable to patients and other staff. Second, a well-designed uniform would reinforce the image that the profession wants to convey: trust, hygiene and...

---

**FIGURE 3: Doctors’ uniform in West Middlesex NHS Trust hospitals: navy blue with ‘Doctor’ printed on the chest pocket.**
competence. Third, a uniform would provide pockets (a not inconsiderable advantage, as anyone who has had to go without the white coat is aware). What would such a uniform look like? Two such possibilities exist in the NHS. Guy’s and St Thomas’ Hospitals in London recently introduced a uniform for all staff, fashioned on the white coat.21 The garment is shorter than a traditional white coat, has short sleeves, large pockets and a zip at the front. Medical students have “medical student” emblazoned on the front, along with the NHS logo. Junior doctors have “Doctor” in big, identifiable writing on the chest, and consultants have their name and specialty embroidered. The coats are laundered by the hospital for staff, much as hospital scrubs are, to maintain hygiene. Another example is West Middlesex NHS Trust, which introduced similar uniforms based on scrubs rather than the white coat, again with the title of the individual labelled clearly (Figure 3).

Conclusion

Many are sorry to see the white coat in its current form disappear, particularly as it is an integral part of the ‘brand’ of being a doctor. However, brands can change, and if the disadvantages of the white coat – be they hygienic or elitist – outweigh their benefits, we should change the brand. There is no reason the white coat cannot be adapted, much as some NHS trusts in the UK have done, to make them acceptable to both patients and doctors alike. However, it is also important to remember that there is more to professionalism than a professional appearance. A professional appearance contributes to a good first impression and helps establish rapport, but professional behaviour is important to continue that, and is ultimately more valued by patients and their families.

References

Electroconvulsive therapy (ECT) is an emotive topic. The debate about its use is one that no one comes to neutral. The above quote by Sylvia Plath is a line from Esther Greenwood, the main character in her novel *The Bell Jar*, as she is having ECT for the first time. It exemplifies the negativity and fear characteristically displayed in popular fiction when the protagonists are faced with the prospect of this treatment. There is no doubt that the stigma still surrounding mental health disorders and their treatment weighs heavily on our society. One treatment that bears the brunt of this stigma is ECT.

Electroconvulsive therapy (ECT) is an emotive topic. The debate about its use is one that no one comes to neutral. The above quote by Sylvia Plath is a line from Esther Greenwood, the main character in her novel *The Bell Jar*, as she is having ECT for the first time. It exemplifies the negativity and fear characteristically displayed in popular fiction when the protagonists are faced with the prospect of this treatment. There is no doubt that the stigma still surrounding mental health disorders and their treatment weighs heavily on our society. One treatment that bears the brunt of this stigma is ECT.

**Safe and effective**

ECT is a relatively safe, effective treatment for severe depression. It uses a small amount of electricity to induce a generalised seizure under general anaesthetic. The seizure is modified by the use of muscle relaxants. The patient is usually given a course of about eight to 12 treatments over a number of weeks. Patients may experience side effects such as acute confusion, headaches and memory loss. Some of the memory loss may be permanent. Stigma is undoubtedly the single greatest obstacle to the appropriate use of ECT.

IOLANDA TIEDT makes the case for this often controversial treatment method.

“I wondered what terrible thing it was that I had done.”

Sylvia Plath, *The Bell Jar*.1
Patients may experience side effects such as acute confusion, headaches and memory loss. Some of the memory loss may be permanent. Stigma is undoubtedly the single greatest obstacle to the appropriate use of ECT.2

While on my psychiatry rotation as a fourth-year medical student, the first patient that I met was Mrs M. She was tearful, apathetic and essentially bedbound due to her crippling depression. She could neither sleep nor eat and was tortured by persistent, inescapable thoughts of killing herself. Although she loved reading, she could not focus enough to do so anymore. She had been in hospital for two months. This was her second admission; she had been hospitalised once before, ten years previously. This time, all of the medications available had been tried – nothing was working. Mrs M was due to start ECT the day after I met her. She was worried but felt that this was her last hope.

Prejudices

Literature and film have often portrayed ECT as a cruel, primitive procedure. Much of the fear surrounding the treatment seems to stem from the misconception that this therapy is portrayed realistically in films such as One Flew over the Cuckoo’s Nest. This is one example of a film that has almost irremediably tarnished ECT’s image. In it, we see a patient undergoing unmodified ECT, i.e., without the use of a general anaesthetic or a muscle relaxant, therefore producing a violent grand mal seizure. This is neither a true representation of the way the therapy is carried out now, nor of how it was carried out in 1975 when the film was released, yet it had a catastrophic effect on the public image of ECT. When we think of ECT in film, it is difficult to come up with positive examples. Instead, our heads are filled with images of institutions like the one in the film Shutter Island. This makes it easy to understand the negativity surrounding this treatment.

The negativity and fear associated with ECT seems out of proportion when compared to public opinion of other medical procedures. For example, in 2011 Senator Niall Ó Brolcháin said he personally believed ECT was “absolutely barbaric”.3 This word, by definition, means savagely cruel, primitive and unsophisticated. These are not words that we are used to associating with modern medicine. The idea of interfering with the brain, the most sacred of organs, in what people perceive as a non-lifethreatening situation, is taboo.

Any form of brain surgery carries this same risk, yet it is ECT that is described as barbaric. Yes, induction of a seizure as a form of treatment seems paradoxical. It could be seen as callous or uncivilised. But is it any more crude than drilling a hole in someone’s skull in order to relieve the pressure caused by a subdural haematoma? Is it more invasive than performing an appendicectomy to treat appendicitis? The scientific answer is no. ECT does carry risks, but the main risk is that general anaesthetic is used. Why, then, is ECT seen in such a negative light when compared to other life-saving procedures? The key words here are ‘life saving’. Perhaps depression is not viewed as life threatening, but this is not the case.4 Perhaps the potential for some memory loss5 post procedure is what scares people the most. We need to weigh up a small degree of memory loss against being trapped in your own mind, unable to care for yourself, with no quality of life and a distinct risk of death. When we do this, I believe that it quickly becomes clear what most people suffering from severe depression would choose.

ECT tends to be viewed more negatively by people who have had little contact with it; knowledge of the procedure is associated with lower levels of fear.6 Most patients experience anxiety about their first treatment. Despite this, a 2005 study by Dowman et al. found that 98% of the patients treated with ECT said that they would avail of ECT if they became unwell again. After having completed the treatment, 62% of patients surveyed found ECT to be less frightening than visiting the dentist. It has been shown that a reduction in fear of ECT was only achieved by a doctor explaining the procedure to the patient.7 For this reason, it is very important that doctors have a thorough understanding and unbiased view of the treatment.

Knowledge of ECT among health professionals

On the first day of my six-week psychiatry rotation, my class was given a lecture on ECT. Up until this point, I wasn’t aware that the therapy was still in use and was shocked by this discovery. Upon conducting research, I found that I was not alone. Healthcare workers’ opinions and knowledge of ECT have been shown to vary hugely. A 2001 study of second-year medical students in the US showed that 40% of those surveyed felt that ECT was misused, and 31% actually thought that it was used as a punishment.8 Another study found that 92% of final-year Hungarian medical students surveyed rated their knowledge of ECT as poor; 35% of this group believed that ECT was used to control violent patients.9 Closer to home, a 2006 study showed that 39% of Irish medical students surveyed thought that ECT could cause brain damage. In the same study, 25% of doctors...
linked ECT and brain damage, and 10% overestimated ECT-related mortality. This study showed even worse figures for nurses. One-third of those surveyed overestimated ECT-related mortality and did not know if it caused permanent brain damage. Only one psychiatric nurse (2.9%) surveyed expressed positive attitudes towards its use. It is important for the healthcare professionals working with these patients to be able to give factual information and reassurance to someone considering the procedure. Is it really surprising that the public has fears about ECT when the professionals responsible for it are so divided in their knowledge and opinions?

Like any other medical procedure that uses general anaesthetic, ECT is a treatment that carries risks. However, it has a higher efficacy than treatment with antidepressant medication. I have come to believe that this treatment can hold the life-changing potential to free a patient from their torment and place them back among the living.

The barbaric procedures displayed by mass media have had a significant negative impact on public opinion surrounding ECT. This, however, does not represent the opinions of those who have actually had the treatment, or the opinions of their friends and relatives. Perhaps if public focus was shifted from the negative aspects of ECT in the past to the positive impact that it can potentially have, the stigma surrounding it would be successfully shaken.

The last time I saw Mrs M, she was tearing herself away from her book in order to go shopping for an outfit for her granddaughter’s christening. If I had not seen her six weeks previously, I would not have believed that this was the same woman. Gone were the thoughts of killing herself. The stifling apathy had lifted. She was playing an active part in the world again, rather than just watching life go on around her. I do not believe that any amount of lectures could have helped me to completely accept ECT. Seeing the change that it brought about in this patient did just that. Perhaps, in an effort to dispel the negativity, those of us who have had exposure to ECT should be more vocal about how positive an experience it can be for patients.

Sylvia Plath best describes the effect of the therapy that we should be trying to highlight, in the quest to throw open the blackout curtain of fear that has been closed over ECT for so long.

“All the heat and fear had purged itself. I felt surprisingly at peace. The bell jar hung, suspended a few feet above my head. I was open to circulating air.” — Sylvia Plath, *The Bell Jar.*

References

The gap between what I expected and the reality of what I had signed up for began to dawn on me soon after I arrived at Kolkata International Airport, mere days after completing my first-year medical exams. Following an exhausting 14-hour train trip and a two-hour drive over monsoon-soaked roads, I arrived at Sewa Bhawan Hospital (SBH), a small rural hospital on the edge of a jungle. For the next two months, under the guidance of Dr Tushar and his wife Dr Kanchan Naik, my appointed mentors, I was thrust into the medical realities of this rural community. The situation was more dire than I could have imagined. I observed with awe as very competent and dedicated medical staff dealt with rural medical demands that would defy possibility in the ‘Western’ hospitals I had been acquainted with to this point.

For starters, I found myself directly involved in assisting in medical procedures that were often beyond my medical knowledge, let alone my comfort level. I had not anticipated routine power outages (even during surgery), severe injuries, poisonings, and sometimes, and most challenging, the unexpected demands of cultural customs that often added to the stress, especially for the uninitiated like myself. However, I couldn’t help but be struck by the professionalism, competence, compassion, and patience of the medical staff. I sensed early on that the level of learning I would attain over the following months would exceed my highest expectation.

**General medicine**

SBH was opened in 1928 as a dispensary to serve the people of the Mahasamund district of Chhattisgarh. Today it is a 50-bed medical facility, and one of 21 hospitals operating under the administrative umbrella known as the Emmanuel Hospital Association (EHA), an organisation committed to providing medical service first and foremost to the poor of rural Northern India. The hospital provides essential healthcare for an estimated population base of nearly 200,000 people across 300 villages. A husband and wife team – one a general surgeon, the other an obstetrician/gynaecologist – comprises the hospital’s only consultants. SBH has the only three operating theatres in the whole catchment area.

SBH is a Christian hospital. Every day begins with morning devotions, with rounds commencing promptly thereafter. The morning rounds provided me with an opportunity to see critically
ill patients and develop postoperative management skills. Once rounds are completed, there is only a quick break for breakfast before the outpatient department (OPD) opens and the usual rush of activity begins.

A common case seen at the hospital is sickle cell anaemia crisis, which is most prevalent during the rainy season, i.e. June to September. Simple measures like childhood vaccinations, adequate oral intake of fluids with electrolytes during vaso-occlusive crises, and avoidance of exposure to extreme temperatures can mitigate the frequency and severity of these incidents. Anaemia, due mostly to malnutrition, is common in pregnant mothers. Malaria from increased mosquito infestation during the rainy season, typhoid fever due to poor water sanitation, scorpion bites, and diabetes were also common presentations.

Traditionally, the focus in developing countries has been on primary prevention of infectious diseases. However, India faces a dual burden of infectious diseases and increasing prevalence of non-communicable diseases such as asthma, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, and psychiatric problems, to name a few. As such, there is an urgent need to formulate appropriate policy responses to these diseases (their prevention, as well as treatment), as they are very expensive to treat and well beyond the means of the poor. A range of effective, population-wide approaches for chronic disease prevention and control exist; however, governments, the private sector and the community must work together and scale up their efforts to reach all members of society.

**Obstetrics and gynaecology**

I had my first exposure to obstetrics and gynaecology under the guidance of Dr Kanchan Naik. Once I became accustomed to terms associated with an obstetric and gynaecological history, I was able to help with multiple deliveries, suture episiotomies, and assist in caesarean sections and tubal ligations. I encountered presentations that would rarely be seen in a Western setting. These included a massive leiomyoma myometrium tumour, foetal death in utero, retained placentas following village deliveries, and advanced cases of cervical cancers and pelvic inflammatory disease. My time in the OB/GYN outpatient department also brought to my attention the very different gender dynamic in India, which from a Western perspective seems incredibly archaic.
In Indian culture, immense pressure is placed on new brides to give birth to a son, as males are more valued than females. It was difficult to become accustomed to this gender inequality. In addition, the husbands and fathers accompanying women to the hospital regarded them as ‘chattels’, and were very involved in directing the medical care they received.

**Ophthalmology**

India has the dubious distinction of having the highest number of blind people in the world - figures vary from 12-15 million. In the majority of these cases, blindness is a result of cataracts, which can be corrected through surgery. Because EHA facilities are, for the most part, located in rural villages, they are able to reach out to the poor and marginalised members of the Indian population; however, there is still a lack of qualified ophthalmologists to service the rural areas. Several hospitals are without a resident eye surgeon to provide continuous year-round service. In spite of this difficulty, 12 EHA hospitals provide some form of eye care, if not year round, then intermittently in the form of hospital-based camps by inviting EHA teams or eye surgeons from other organisations. I was fortunate enough to observe a visiting ophthalmologist perform cataract operations during one of these eye camp services. Unfortunately, many people do not reach the EHA eye care clinics; some people are still unaware of the availability of services, or are inhibited by fear of surgery, the cost of surgery or other social handicaps.
Mental health
One day, while I was out playing soccer during a recreational opportunity, one of the hospital staff members called the junior doctor and me to the intensive care unit.
A quick history and examination revealed a family of five all in cholinergic crisis. Organophosphate poisoning is common in developing countries, and especially so in India. Often poisoning occurs by voluntary ingestion, according to a study conducted by the Indira Gandhi Institute of Development Research, Mumbai.
Major reasons for farmer suicides via organophosphate ingestion are linked with: the inability to pay debt; crop failure and low returns; illness of family members; failure to arrange the marriage of daughters; and, a lack of alternative sources of income. Unfortunately, this was not an isolated case. During my two-month stay at the hospital, I witnessed over 10 patients suffering from the same presentation.
The EHA is in the process of performing a research study with the intent of developing a greater understanding of the underlying causes and possible remedies of this tragic phenomenon, in order to offer support and counselling. Due to a lack of human resources and inadequate infrastructure, mental health services are far less available in rural than urban areas; where they are available, financial constraints and social issues still act as barriers to access.

Concluding thoughts
Hospital administration is a major challenge in the present day environment of private and corporate hospitals, where demands from the community are ever increasing. Most Indians seek healthcare in private facilities, as public facilities often suffer from a variety of problems. These include: worker absence and dual public-private practice; low demand for their use; and, shortages of supplies and staff.
In contrast, private healthcare varies greatly in quality across centres, as it is unregulated and financed largely through out-of-pocket payments. Smaller rural hospitals face the challenges of staff retention and financial sustainability, as they
continue to fulfil their mission of serving the poor. Despite this, the number of patients seen in EHA hospitals has been increasing. The implementation of national health insurance coverage for below-poverty-line families known as Rashtriya Swasthya Bima Yojana (RSBY) has enabled EHA hospitals to provide greater care to those in need. From my limited experience, my impression is that, while India is moving forward as a developing nation, it has yet to fully educate its rural population in matters pertaining to personal healthcare. The dilemmas they face have as much to do with complex social barriers and long-held beliefs and customs that interfere with progress, as with limited medical resources for a rapidly expanding population. I remain optimistic, given the resourcefulness and commitment of the medical personnel that I worked with during my placement, that India will one day be able to address these challenges more successfully.

References

Most students will be familiar with the story of the discovery of penicillin: a hurried microbiologist by the name of Alexander Fleming left a petri dish unwashed in the lab as he left for his holidays. To his surprise, on his return he found that a fungus had grown, which had killed nearby colonies of the Staphylococcus bacteria. What followed was the extraction of penicillin from the fungus, which revolutionised the treatment of infectious diseases and dramatically reduced mortality from infection. What many people may not be familiar with is that, had this accident happened in any other lab in Britain, it is likely that penicillin never would have been discovered. Penicillium notatum – the fungus that colonised the petri dish – had wafted up to Fleming’s laboratory from the laboratory below during a particularly cool period in London, which provided the perfect growth environment for the fungus to kill the bacteria. This perfect storm of unlikely events resulted in millions of lives saved from infectious diseases over the following years.

This anecdote captures the message of The Rise and Fall of Modern Medicine: that the major medical discoveries of the 20th century have resulted from a delicate balance of ingenious logical thinking and serendipity.

The rise
James Le Fanu made his name as a medical historian with his columns in the Daily and Sunday Telegraph, The Times, The Spectator, and GQ magazine. In this, his third book, he charts the course of modern medicine through his ‘12 definitive moments’: developments in fields such as surgery, epidemiology, oncology and psychiatry that transformed these specialties into the modern practice we know today. As he takes us through the last century, we meet the people who translated casual observation about nature into medical theories; those who strove to make advances in one area and stumbled into discoveries in another; and those who were in the right place at the right time.

The fall
The confidence crafted in the first half of the book is challenged in the second as Le Fanu follows the ‘fall’ of modern medicine, citing the decline of new drug discoveries and the new ethical challenges posed by the 20th century’s rapid medical developments as factors leading to the end of medicine’s golden age. He skillfully identifies the hurdles that contemporary medicine will have to overcome if it is to prevent the momentum built by the previous century from grinding to a halt.

More history than science, this book is essential reading for anyone who has ever wondered how medicine functioned before many of our modern therapies, and the elegant solutions to some of the most dangerous diseases, were developed. The Rise and Fall of Modern Medicine grounds many of the biological and clinical sciences we learn in medical school in a historical and social context, and puts names and backgrounds to established therapies and interventions we may take for granted. It is a well-written, accessible book, which can be as easily read from cover to cover in one session, as it can be dipped into over time. Le Fanu’s impression of the future of medicine provides ample food for thought for both junior medical students beginning their studies of disease, and senior students about to enter clinical practice.
Volume of caudate nucleus in major depressive disorder

Sarah Pradhan
RCSI medical student

Background
Major depressive disorder (MDD) is a disabling illness affecting 15-20% of people worldwide. It is characterised by low self-esteem, high self-criticism, symptoms of melancholia and suicide attempts. Studies have shown the caudate nucleus to be important in emotion and reward, as emotional networks are localised to the head of the caudate. In depressed adolescents, smaller caudate nuclei volumes have been noted. Therefore, a smaller caudate nucleus may be present in adult patients suffering from MDD, as proposed by other studies.

Methods
This study included 19 healthy controls (eight males and 11 females, aged 20-52) and 51 patients with MDD (18 males and 33 females, aged 19-58), who underwent magnetic resonance imaging (MRI). Volume of the caudate nuclei was determined by performing manual tracing on MRI images using AnalyzeDirect 10.0 operated by a trained and reliable rater (SP, r=0.93-0.99).

Results
No significant differences were found between healthy controls and patients with MDD in the right (t=0.058, df=65, p=0.954), left (t=0.014, df=65, p=0.989) and total caudate volumes (t=0.024, df=65, p=0.981). No significant difference in the asymmetry of the caudate was observed in patients with MDD versus healthy controls (t=0.187, df=65, p=0.852). Furthermore, in the patients with MDD, right caudate volume correlated with the change in depression scores with treatment (r=0.34, p=0.036). Interestingly, when the MDD group was divided into treatment responders and non-responders, a trend for larger right caudate volumes in the responder group was observed, although this did not reach statistical significance (t=1.77, df=37, p=0.086).

Conclusion
This data suggests that right caudate volume may be predictive of treatment response. Studies have shown the right caudate nucleus to have greater availability of dopamine than the left; thus, the right caudate could be more sensitive to treatment. However, this requires further investigation. Although significant volumetric differences between patients with MDD and controls were not found, reasons for this may include small sample size, differing methods of caudate measurement or medication history.

References
ABSTRACT SUBMISSION OPEN SOON!

Join us on October 24th and 25th 2014

RCSI Royal College of Surgeons in Ireland, Dublin.

Oral and Poster Presentations, Workshops, Keynote Speakers, Social Programme and much more.

For more information, visit: www.ichams.org