The British Student Doctor Journal
BSDJ
VOLUME 3, No.2
30 June 2019
ISSN 2514-3174
bsdj.org.uk

The dead shall entertain the living:
'Bodyworlds' from the perspective of medical students

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Journal DOI
10.18573/issn.2514-3174

Issue DOI
10.18573/bsdj.v3i2

Cardiff University Press
Gwasg Prifysgol Caerdydd

The British Student Doctor is an imprint of Cardiff University Press, an innovative open-access publisher of academic research, where 'open-access' means free for both readers and writers.

cardiffuniversitypress.org

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doi: 10.18573/bsdj.113
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Editorial

Dr James M. Kilgour
Co-Founder & Editor-in-Chief
The British Student Doctor
Oxford University Hospitals NHS Foundation Trust

ORCID: 0000-0001-8067-2306

Dr Eleni Panagoulas
Senior Editor
The British Student Doctor
Imperial College NHS Trust

ORCID:0000-0001-5920-1024

Address for Correspondence:

Editors-in-Chief
The British Student Doctor Journal
PO Box 430
1st Floor, 30-36 Newport Road
Cardiff, CF24 0DE

Email: editorinchief@bsdj.org.uk

No conflicts of interest to declare

Accepted for publication: 21.06.19

Welcome to the June 2019 issue of *The British Student Doctor*!

This issue features two guest editorials on the changing face of undergraduate medical curricula. In the editorial, "*INSPIRing medical undergraduates*", Dr Sam Hinder and colleagues at Keele University pioneered a summer internship programme to encourage medical student participation in research. The article features the thoughts of three Keele students who completed the programme, describing their experiences and what they gained from their unique studentships.

Continuing this theme of the evolution of medical curricula, our second editorial introduces the importance of medical leadership in medical education. Leadership has been "*enshrined*' by the GMC in their 2018 "*Outcomes for Graduates*" document, and the importance of the Faculty of Medical Leadership and Management (FMLM) in guiding this development is discussed. The authors also highlight potential opportunities for medical students to begin their journey in medical leadership.

The Discussion section of this issue deals with two very contentious issues. Firstly, in "*Is the pharmaceutical industry overpowering the medical profession?*" Nazia Din and Maria Kordowicz from King's College London present a potential vision for cooperation between pharmaceutical companies and doctors, in a way that would not compromise patient care. In the latter, Saloni Patel from the University of Oxford, presents an astute legal argument about a "*rights based*" approach to decisions involving issues such as euthanasia and organ and tissue donation.

In the Education section, we feature an article by Sara Gritti from the University of St Andrews. It highlights the research gap into the consequences of exposure to cannabis on foetal and neonatal development. This article is particularly informative and extremely topical, given the recent spread of legalisation of cannabis throughout many parts of the world. Our second Education article, written by Anastasia Mirza-Davies and Dr Judith Harrison from Cardiff University, discusses the next generation of imaging in neuroscience research.

In our final section, Reflections, Emma Jane Norton and Harry Davies from St George's, University of London, reflect on the ethical issues surrounding the controversial use of plastination and cadavers for their shock factor and entertainment value rather than for education. Our final Reflection piece, by Dr Mustafa Abdimalik, sensitively touches upon how difficult it is caring for patients with dementia, as frequently the good intentions of medical professionals can be misunderstood by the patients, who may feel threatened by invasive procedures such as intravenous cannulation.

We hope that you will enjoy this issue as much as we have enjoyed curating and editing it. As always, we extend our gratitude to our hard working and dedicated editorial team, peer reviewers, faculty advisory board and our publisher, Cardiff University Press. If you would like to contribute to our next issue, our full author guidelines are available on The BSDJ website. We look forward to publishing our next issue in January 2020.

The British Student Doctor, 2019;3(2):2-5
doi: 10.18573/bsdj.110
Editorial

Guest Editorial

Dr Samantha Hider
Research Institute for Primary Care and Health Sciences
Keele University
Haywood Academic Rheumatology Centre
Midlands Partnership Foundation Trust

Beth Seale
School of Medicine, Keele University

Dr Arani Vivekanatham
School of Medicine, Keele University

Will Woods
School of Medicine, Keele University

Professor Divya Chari
School of Medicine, Keele University

Address for Correspondence:

Dr Samantha Hider
Primary Care Centre Versus Arthritis
Primary Care Sciences
Keele University
Staffordshire, ST5 5BG

Email: s.hider@keele.ac.uk

No conflicts of interest to declare

Accepted for publication: 10.06.19

Awareness and understanding of research are both increasingly important for medical undergraduates, with the General Medical Council's Outcomes for Graduates stating that medical students in the UK must be able to "*apply scientific method and approaches to medical research*". (1) Critical analysis and interpretation of research is key to applying the evidence-based medicine required for clinical practice. The impact of research on clinical practice is highlighted by NHS England: "*Research is vital in providing the evidence we need to transform services and improve outcomes*". (2) Studies highlight that undergraduate engagement in research helps develop transferable skills such as critical appraisal, (3) together with developing presentations and publications. (4) Furthermore, undertaking a research-oriented programme influences later academic career choice. (5)

However, engagement with research as an undergraduate is not without challenges. A recent systematic review examining global perspectives of medical students towards research showed that students expressed positive attitudes towards research, but identified barriers such as time, lack of mentorship and financial considerations. (6) Whilst intercalation remains a popular choice for many undergraduates, financial considerations and rising graduate entry schemes mean that there is increasing interest in shorter research placements. The reasons for this include to gain a "*taster*" of research and engage with CV enhancing activities such as research presentations and opportunities for publication.

With this in mind, in 2013 we established a summer research internship scheme to provide Keele medical undergraduates much needed opportunities to engage in research. Whilst organisations (e.g. Wellcome Trust and NIHR School for Primary Care) offer short research internships, the lack of funding support for short student projects presented a critical challenge, particularly for a young medical school such as Keele. We gained initial funding in 2013 from INSPIRE- a national scheme funded by the Academy of Medical Sciences and Wellcome Trust, which aims to engage medical undergraduates with research. (7) This enabled us to establish a summer research internship scheme (4-8 weeks) where students identify projects via a specially designed database and undertake their first piece of medical research. The projects are wide ranging-from laboratory, medical humanities and medical education to clinical research (both primary care and hospital based) and can be qualitative or quantitative. Other activities have included the development of the student medical research society, student-researcher networking events, and award of conference bursaries. Successful students present at an Annual Medical School Research Showcase featuring talks from eminent invited speakers, gaining experience of both poster and oral presentations. Critically, gaining external grant support enabled leverage of additional funding from the University, local medical charities such as the North Staffordshire Medical Institute, enabling the scheme to expand whilst ensuring financial sustainability; this is a key consideration in challenging financial times for universities. In 2014, we received funding support from the EPSRC Doctoral Training Centre for Regenerative Medicine, allowing students to undertake projects in collaboration with industrial partners. In 2018, we successfully bid for our third national INSPIRE award.

The scheme overall has been popular and highly successful, with 79 projects

funded to date, including in world leading Brasilian Dengue/Zika research groups. The experience is highly rated by students (Table 1) who emphasised the value of the opportunity to collaborate with academics, gain academic mentoring, learn new techniques and contemplate career opportunities not previously considered.

Figure 1: Student volunteers at the aspire research showcase

- *The studentship experience has been extremely valuable, as well as challenging at times. I have not only learnt a lot about qualitative research but also a lot about myself as a future medical professional.*
- *...the studentship provided me with an opportunity to use lab techniques and equipment that I haven't been able to use up until now.*
- *...the placement provided a valuable insight into a research-based career...*

Table 1: Feedback from students undertaking summer studentships

There have been additional benefits for early career staff researchers in gaining supervision experience working within teams. Key outputs for students have included presentations, regionally and nationally, with several students winning conference prizes and more than ten students publishing their work.

Importantly it has been the start of a research career trajectory for students, with some students going on to intercalate (Case Study 1 & 2) and influencing career choices such as academic foundation posts (Case Study 2) and academic careers long term (Case Study 3).

Case Study 1: Will Woods (Studentship 2018)

I gained valuable insight into carrying out research and learnt advanced laboratory skills such as cryosectioning and immunostaining. I presented my data at the Keele ASPIRE conference and was awarded 1st poster prize. The time spent during this project was enjoyable and rewarding as well as providing multiple further research opportunities including a Neuroscience intercalated

MPhil position in 2019. The ASPIRE scheme has given me invaluable experience, enabling me to explore and affirm my passion for neurology and skills to further a career in academia and strengthen my portfolio for future job applications.

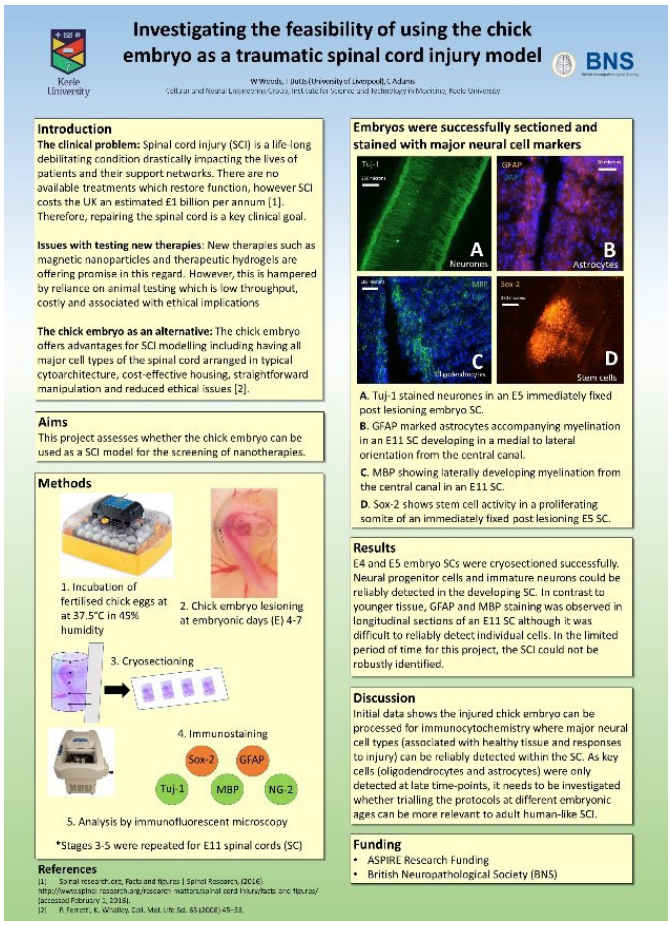

Figure 2: Prize winning poster 2018

Case Study 2: Beth Seale (Studentship 2015 and 2017)

The ASPIRE scheme provided excellent research experience and ultimately inspired me to undertake an intercalated MPhil (due to complete 2019). The rigorous research training undertaken has helped me decide on my future career path, and I am applying to the Academic Foundation Programme and hope to eventually combine clinical work and academia. I do not think I would have taken this path without the opportunities provide to me through the Studentship scheme.

Case Study 3: Arani Vivekanatham (Studentship 2013)

Undertaking a Keele ASPIRE studentship scheme in my 3rd year of medical school not only allowed me to develop invaluable research skills in a supportive environment, but also gave me an insight into life as a clinical academic early on in my career and led to opportunities (e.g. a poster tour presentation at the British Society of Rheumatology conference, an Arthritis Research UK essay prize and first author publication in a peer review journal), which has been instrumental in helping me to develop a clinical academic career in Rheumatology. I am now an NIHR Academic Clinical Fellow in Rheumatology and believe my successes to date have stemmed from the fantastic opportunities and supervision from the studentship scheme.

The development of the Keele Summer Internship Scheme, which funds medical undergraduates to undertake a short period of research has been highly successful. In addition, summer Internship Scheme, which funds medical undergraduates to undertake a short period of research. In addition to developing individual research skills via presentations and publications the scheme has had a clear impact on career aspirations and successes in building academic career trajectories, with students going on to do further research via intercalation and academic foundation posts. The long-term impacts of the scheme require further study.

References

1. General Medical Council. Outcomes for Graduates; 2018. London: General Medical Council (UK) [accessed 25 April 2019]. Available from: https://www.gmc-uk.org/education/standards-guidance-and-curricula/standards-and-outcomes/outcomes-for-graduates.

2. NHS England. NHS England Research Plan; 2017. London: NHS England [accessed 25 April 2019]. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/nhse-research-plan.pdf.

3. Naing C, Wai VN, Durham J, Whittaker MA, Win NN, Aung K, Mak JW. A Systematic Review and Meta-Analysis of Medical Students' Perspectives on the Engagement in Research. Medicine (Baltimore). 2015;94(28):e1089.

https://doi.org/10.1097/MD.0000000000001089

PMid:26181541 PMCid:PMC4617066

4. Cursiefen C, Altunbas A. Contribution of medical student research to the Medline-indexed publications of a German medical faculty. Med Educ. 1998;32(4):439–40.

https://doi.org/10.1046/j.1365-2923.1998.00255.x

PMid:9743810

5. Borges NJ, Navarro AM, Grover A, Hoban JD. How, when, and why do physicians choose careers in academic medicine? A literature review. Acad Med. 2010;85(4):680-6.

https://doi.org/10.1097/ACM.0b013e3181d29cb9

PMid:20354389

6. Stone C, Dogbey GY, Klenzak S, Van Fossen K, Tan B, Brannan GD. Contemporary global perspectives of medical

students on research during undergraduate medical education: a systematic literature review. Med Educ Online. 2018;23(1):1537430.

https://doi.org/10.1080/10872981.2018.1537430

PMid:30372403 PMCid:PMC6211259

7. The Academy of Medical Sciences. The INSPIRE scheme. London: The Academy of Medical Sciences; 2013 [accessed 25 April 2019]. Available from: https://acmedsci.ac.uk/grants-and-schemes/mentoring-and-other-schemes/INSPIRE/awards.

8. Vivekanantham A, Protheroe J, Muller S, Hider S. Evaluating on-line health information for patients with polymyalgia rheumatica: a descriptive study. BMC Musculoskelet Disord. 2017;18(1):43.

https://doi.org/10.1186/s12891-017-1416-5

PMid:28122554 PMCid:PMC5267405

The British Student Doctor, 2019;3(2):6-8
doi: 10.18573/bsdj.106
Editorial

Guest Editorial

Professor Judy McKimm
Professor of Medical Education and Director of Strategic Educational Development
Programme Director MSc in Leadership for the Health Professions
Swansea University School of Medicine
Swansea University

Paul Kneath Jones
Honorary Associate Professor
Programme Director Graduate Entry Medicine (GEM) Programme
Programme Director MSc in Leadership for the Health Professions
Swansea University School of Medicine
Swansea University

Dr Claire Vogan
Associate Professor
Lead for Student Support and Guidance, Graduate Entry Medicine (GEM) Programme
Swansea University School of Medicine
Swansea University

Address for correspondence:

Professor Judy McKimm
Swansea University School of Medicine
Grove Building
Swansea University
Singleton Park
Swansea
Wales, SA2 8PP

Email: j.mckimm@swansea.ac.uk

No conflicts of interest to declare

Accepted for publication: 16.04.2019

It is very timely to write about leadership in relation to medical students, as the Faculty of Medical Leadership and Management (FMLM) has recently published new guidance for educators working in undergraduate medicine on medical leadership (1) which sits alongside its Leadership and Management Standards for Medical Professionals (2nd edition). (2) The General Medical Council has also enshrined competencies around leadership and management more firmly into Outcomes for Graduates 2018. (3) The aim of this latest guidance is to integrate leadership, management and followership into the very crowded medical curriculum in a way which has not been attempted before, although guidance for medical educators has been around since the publication of the Medical Leadership Competency Framework in 2008. (4)

What is medical leadership?

Over the last ten years, a shift has occurred in the way leadership is viewed, what leadership behaviours are the most appropriate for health professionals to display, and its importance for all doctors. Doctors have always taken clinical leadership based around their accountability for patient care. However good leadership and management are central to health improvements and patient safety (5) and the role of doctors in healthcare leadership and management is increasingly recognised and promulgated. (6)

Medical leadership comprises three core skill sets – the '*leadership triad*': (7)

• Management is about planning, providing stability and order, including self and time management, but also prioritising and using resources efficiently;

• Leadership is about change, setting direction and adaptability. Organisations, teams or situations need both leadership and management in varying amounts depending on the context. For example, in a cardiac arrest, someone needs to take the lead, but it is vital that all equipment and drugs are available when needed;

• Followership is about being supportive, active, questioning and helpful. This is important to ensure groups, teams and departments function smoothly. Sometimes you will need to be a '*passive*' follower, take instructions and be unquestioning, at other times you might need to be more active and challenging – it can be a hard balance.

Leadership practice and development happens at three levels. (8) As a medical student, it is important to get to know yourself, develop self-insight and emotional intelligence, understand your strengths and weaknesses, and your responses under pressure – this is the intrapersonal level. You can do this by undertaking self-development activities, many free ones are available online, or your School may already include self-development activities in the curriculum. Particular leadership qualities include emotional intelligence, resilience, grit and compassion. As a developing leader, you will be working in teams - with other people, patients and colleagues, learning how you are seen by others through conversation and feedback. This is the interpersonal level. One way your School might seek to gain formal feedback is through multisource feedback from peers and teachers. Although it can feel confrontational at times, this can also be very helpful for your development, particularly if different people are saying the same things. At the organisational or system level, leadership involves learning about and understanding the wider systems and organisations in which you work, including procedures and processes and how change and quality/service improvement may be managed.

It is very hard to lead when your personal or positional power and influence is low. But, you can develop more credibility by understanding the healthcare system in which you work, and, if you are involved in educational developments at your School, making sure you understand the system and jargon. You also might find that you can become an expert (even if temporarily) in your area, project or initiative and this will help build your credibility. You can learn more about leadership through what Petrie (2014) calls '*horizontal leadership*', which gives you an evidence base (in terms of theories, concepts, models and tools) about what leadership is, how it works and ways of approaching situations or tasks, and '*vertical leadership*'. (9) Petrie suggests that this comprises three elements: meeting challenges ('*heat experiences*'); '*sense-making*' of the experience (through reflection and conversation) and being open to '*colliding perspectives*' about what is going on.

What does this mean for undergraduate programmes?

The UK plays a leading part in the conceptualising and implementation of medical and clinical leadership. For example, '*Outcomes for Graduates 2018*', the GMC's new standards for medical graduates (against which all UK medical programmes are approved), sets this out very clearly as a core part of professional knowledge and behaviours, expecting all medical students to understand some leadership theories and models and apply these in practice through appropriate behaviours. (3) Alongside this new emphasis, graduates are also expected to understand the health systems in which they work and to be able to carry out quality and patient safety improvements. Through these measures it is hoped that future doctors will be able to make a much more informed contribution to healthcare leadership and management. UK medical students should therefore expect to see an increasing emphasis on and routinisation of the teaching and learning (and assessment) of professionalism, leadership and quality improvement, rather than simply offering student selected components in leadership and management. (10)

Further opportunities

For those of you who have a deeper interest in these subjects, a number of opportunities are available outside the formal undergraduate course for medical students (and doctors in training) to develop your leadership and management skills further. For example, the FMLM has a very active medical student group (each medical school should have a student representative) and also offers electives in leadership and management (see 'Useful sources of information' below). Once you graduate, the range of options to learn more about medical leadership increases. In addition to mandatory courses offered to all doctors in training (which vary by region and country), leadership and quality improvement fellowships are widely available, some of which include bursaries for undertaking more formal postgraduate degree programmes, and loans and bursaries are available from universities for Masters' level programmes. Finally, each of the four nations has national leadership programmes (see below for links) for doctors at various levels.

In summary, doctors need leadership, management and followership understanding and skills in order to lead meaningful healthcare and quality improvements as well as being a leader in clinical situations. Most management skills can be learned (e.g. project or budget management) and whilst some leadership qualities might be partly innate, they can be modified through a combination of horizontal and vertical leadership development. Leadership practice and development therefore needs to

be evidence based, theory informed and practice driven and many opportunities exist for medical students to develop their leadership skills.

References

1. Faculty of Medical Leadership and Management. Medical leadership and management: an indicative undergraduate curriculum. 2011. London: Faculty of Medical Leadership and Management.

2. Faculty of Medical Leadership and Management. Leadership and management standards for medical professionals. 2016 (2nd ed.). London: Faculty of Medical Leadership and Management.

3. General Medical Council. Outcomes for graduates. 2018. GMC: London [accessed 22 Dec 2018]. Available from: www.gmc-uk.org/-/media/documents/dc11326-outcomes-for-graduates-2018_pdf-75040796.pdf

4. Academy of Medical Royal Colleges and NHS Institute for Innovation and Improvement. Medical Leadership Competency Framework, Enhancing Engagement in Medical Leadership. Coventry. 2010. NHS Institution for Innovation and Improvement: Coventry. Available from: https://www.leadershipacademy.nhs.uk/wp-content/uploads/2012/11/NHSLeadership-Leadership-Framework-Medical-Leadership-Competency-Framework-3rd-ed.pdf

5. West M, Armit K, Loewenthal L, Eckert R, West T, Lee A. Leadership and leadership development in healthcare: the evidence base. 2015. London: The Kings Fund.

6. General Medical Council. Leadership and management for all doctors. 2012. GMC: London [accessed 22 Dec 2018. Available from: www.gmc-uk.org/-/media/documents/leadership-and-management-for-all-doctors---english-1015_pdf-48903400.pdf

7. McKimm J, O'Sullivan H. When I say… leadership. Medical education. 2016;50(9):896-897.

https://doi.org/10.1111/medu.13119;

PMid:27562889

8. Swanwick T, McKimm J. 'Faculty development for Leadership and Management', in Steinert, Y (ed), Faculty development for the Health Professions: a focus on research and practice, Springer; 2014.

9. Petrie N. Vertical leadership development–part 1 developing leaders for a complex world. 2014. Center for Creative Leadership [accessed 16 Apr 2019]. Available from: https://www.ccl.org/wp-content/uploads/2015/04/VerticalLeadersPart1.pdf

10. Till A, McKimm J, Swanwick T. Twelve tips for integrating leadership development into undergraduate medical education. Medical teacher, 2017; 1-7 [accessed 16 Apr 2019]. Available from: http://www.tandfonline.com/doi/full/10.1080/0142159X.2017.1392009

https://doi.org/10.1080/0142159X.2017.1392009

PMid:29073824

Useful sources of information

Faculty of Medical Leadership and Management (FMLM) - https://www.fmlm.ac.uk

NHS Improvement - https://improvement.nhs.uk

NHS Leadership Academy (England) - https://www.leadershipacademy.nhs.uk

Health Education and Improvement Wales - https://heiw.nhs.wales/

Academi Wales - https://academiwales.gov.wales/

NHS Education for Scotland - https://www.nes.scot.nhs.uk

Northern Ireland Medical and Dental Training Agency http://www.nimdta.gov.uk/adept/

The British Student Doctor, 2019;3(2):9-18
doi: 10.18573/bsdj.49
Discussion

Is the pharmaceutical industry overpowering the medical profession?

DISCUSSION

AUTHORS

Nazia Din
Medical Student, King's College London

Dr Maria Kordowicz
Master's in Public Health Course Lead, King's College London

Address for Correspondence:

Nazia Din
King's College London, GKT School of Medicine, Hodgkin Building, Newcomen Street, London, SE1 1UL

Email: nazia.din@kcl.ac.uk

No conflicts of interest to declare

Accepted for publication: 30.12.18

ABSTRACT

Doctors' reported loss of autonomy in the current policy climate and the subsequent deprofessionalisation of medicine can be attributed to many factors. The pharmaceutical industry accounts for a large proportion of healthcare costs, with the professional relationship between the industry and medical profession raising ethical concerns. Developing potentially life-saving products and potentiating scientific advances are some of the many good attributes of the pharmaceutical industry. The dependence of medical care on the production of pharmaceuticals is undeniable. However, it could be argued that the pharmaceutical industry takes advantage of this relationship, fuelled by financial motive. Conversely, there could be a complex interplay of factors driving a power imbalance in the pharma/clinical relationship. By reviewing literature in the field, this viewpoint article explores these multifaceted factors.

Medical students are to enter a profession at the forefront of improving the health of individuals and populations. Scientific innovation, particularly in the field of the pharmaceutical industry, is one of the exciting ways through which physicians are able to practise medicine through prescribing. However, with an increasing array of drugs available, it is important for newly qualified doctors to be able to navigate their way through pharmaceutical industry marketing to ensure optimal clinical practice. (1)

In the past, healthcare was dominated by a paternalistic approach, with people having little access to the medical knowledge held by doctors. (2) The advent of technology and a shift in attitude has resulted in a more informed public, who expect to be involved in decisions affecting their care. (3) For doctors, this means patients are possibly more accountable for their own health, but potentially less trusting of the medical profession. (3) (Haug, 1973) predicted professionals will lose "*their monopoly over knowledge, public belief in their service ethos and expectations of work autonomy and authority over the client*". (4)

Barriers that prevent the profession from carrying out its moral duty to improve the health of general society could reduce professional autonomy. The industry may encourage reliance on prescribed medication, thereby changing the way society responds to health problems and creating a market for products beyond health needs. (5) This article will explore the extent of the influence of the pharmaceutical industry on the medical profession. The Government and governing bodies have an impact on drug availability, as well as prescribing practitioners. Market forces, patient demand and drug development costs may justify its presence and influence in society.

The Government

It could be argued that governmental policy encourages pharmaceutical influence over the medical profession. Foucault states "*the first task of the doctor is political: the struggle against disease must begin with a war against bad government*". The Government negotiates with the pharmaceutical industry to decide the availability of patented or generic drugs for prescription, as well as enforcing caps and budget restrictions on the profession. (6) Most recently, The National Institute for Health and Care Excellence (NICE) has set a cap on drugs costing more than 20 million pounds a year, which is a breach of a pledge made in the Conservative Party's manifesto. (7) The Government also introduced General Practice budgets in 1991 as an attempt to contain growth in NHS expenditure on prescribed drugs. (8) Therefore, the Government may actually be a driver of the pharmaceutical industry's profits in the UK.

Conversely, 2009 Patient Access Schemes have been introduced, offering price reductions on drugs which were unlikely to meet NICE's cost-effectiveness criteria. (9) Therefore, the presence of governmental policy and evidence-based medicine could contain the industry, protecting the professional power of the medical doctor.

NHS and NICE

NICE is an important source of guidance for the use of health technologies within

the NHS and considers both the medical and economical indications. Therefore, NICE ultimately determines the influence of the pharmaceutical industry. The NHS Constitution states patients have the "*right to drugs and treatments recommended by NICE if their doctor believes they are clinically appropriate*". The NHS is therefore legally obliged to fund and resource medicines recommended by a NICE technology appraisal within three months of the published appraisal. (10,11) This legal obligation empowers the pharmaceutical industry to create drugs, which they know will have to be provided (if clinically appropriate). It may also give patients a sense of entitlement to medication that may not be commonly prescribed, for instance by lacking an evidence-base for its efficacy. Patients may feel they can challenge or pressurise their doctor into prescribing medications due to the presence of the publicly funded NHS through general taxation.

Conversely, NICE may be enabling the pharmaceutical industry. The World Health Organisation (WHO) Report was critical of the pharmaceutical industry's influence on NICE, particularly expressing that manufacturers should not be members of the drug appraisal committee. (12) By allowing manufacturers into this committee, NICE could be influenced to approve drugs endorsed by those manufacturers. This may undermine the regulatory system in place for NHS prescribing and potentially take advantage of NICE's position in developing public health guidance, with guidelines being shaped by the financial interests of pharmaceutical industry shareholders.

The role of NICE could be challenged with the impending exit of the United Kingdom from the European Union. Currently, NICE is a lead partner in the European Network for Health Technology Assessment and therefore has a global influence. Although there is much uncertainty regarding the details of this at present, there will be relocation of the European Medicines Agency away from London. This will affect the evidence base for Health Technology Assessments due to less access to European research funding, as well as possibly increasing the cost of medicines and healthcare due to the expense of doing business as a small country. (13)

It can be seen that the availability of possibly life-saving medication has become increasingly dependent on economic factors, especially in a resource-poor public-sector climate. It is considered a doctor's decision to recommend treatment if deemed appropriate, but there are several notable cases where such clinical decisions have been undermined or delayed. Notably, NICE rejected trastuzumab emtansine (Herceptin) for use in the NHS for advanced breast cancer in 2015 for the sole reason of it being too expensive. The drug was reinstated after a deal was made with the manufacturer Roche. (14) The drug lumacaftor-ivacaftor (Orkambi) for cystic fibrosis has also been denied for reasons of cost-effectiveness, despite doctors predicting possible benefits for over 3000 patients, with reductions in hospital admissions and antibiotic use. (15, 16)

Prescribing patterns

It may be the medical profession itself encouraging the pharmaceutical industry.

Medication costs the NHS over 7 billion pounds a year. (17) According to NHS Digital "*In 2016 there were 1,104.1 million items dispensed, which is an increase of 1.9 per cent (20.5 million) on the number dispensed in 2015*". (18) In Britain, increased prescribing powers have been granted to nurses as they are allowed to prescribe independently in the community, within their area of competence or as part of an agreed plan by a doctor. (19) This could result in a greater number of drugs being issued to patients.

Liberal prescribing patterns encourage the pharmaceutical industry, creating demand and financial motive to produce more medication. In doing so, the NHS is promoting an ideology that drugs can solve health problems as opposed to targeting the cause of a disease through prevention strategies. Although general health in society has improved over time, this has not been largely accounted for by the greater use of medicines, therefore proving the theory that drugs do not cure disease. (20)

Evidence-based medicine

The use of scientific research in clinical practice through evidence-based medicine is well-established in healthcare through clinical guidelines. This uses scientific evaluation of research literature to guide clinicians on how to practise medicine. (21) There is a correlation between medical advances and professional decline. This is due to the automation of medical procedures, such as using sound waves instead of scalpels to treat kidney stones, which threatens physicians as '*operators*' as opposed to masters of their technology. (22)

The presence of evidence-based guidelines could deprofessionalise medicine by taking away a clinician's choice and pressurising them to practise medicine in a particular way. This could work in the favour of pharmaceutical companies, especially when using evidence in clinical trials.

The pharmaceutical industry is in a unique position as it can use scientific evidence to serve its own interests, especially in the pre-approval stage of drug development. Initial drug testing is carried out by laboratory scientists or pharmacologists, employed by pharmaceutical companies themselves. This means they could selectively use the information found when seeking approval for new drugs. (23) It is therefore important for professionals to carefully consider information supplied by drug companies and the media.

Pharmaceutical companies can also influence doctors to prescribe specific drugs based on incentives, such as free samples. This could lead to a loss of trust and autonomy in the profession. The industry is able to educate and advise on the latest drugs, although this information is unregulated. Educating prescribers is important, however ensuring this information is accurate and balanced will allow professionals to make well-informed decisions. (24)

Market forces

There is a rise of corporatisation within healthcare, with greater access to private healthcare in the UK than ever before. (6) This could create a societal divide in terms of those who receive medication, encouraging a feeling of entitlement to medication regardless of what the doctor thinks.

It was recognised that biologic drug spending was rising; biosimilars were therefore reverse-engineered to reduce costs. (25) It may be that high drug cost is temporary and will be driven down to become more affordable for the NHS. Market changes are expected and may be a challenge to the medical profession that it will have to adapt and adjust to accordingly.

An economic evaluation of biologics suggests acceptable cost-effectiveness in the long-term due to stabilising disease to reduce costly inpatient surgery care, which accounts for "*44% of the lifetime costs for a typical patient*" with Crohn's disease. (26) This justifies the expense of these drugs, while also proving a positive effect to society.

Some medication patented in the developed world is copied in developing countries, where patent rights of pharmaceutical products are not protected. (27) Therefore, manufacturers who have spent money on developing these products are outcompeted when it comes to selling them. This is troublesome to manufacturers' profits, although perhaps enables the medical profession as drugs can be provided at a fairer price to society.

Research and development

Drug research and development (R&D) is often expensive and timely, which means companies often have to charge high prices to the medical profession to cover their costs. The pharmaceutical industry may use this financial motive to influence the prescription of certain medications.

It can take 10-15 years for drug approval after multiple phases of trials. Data conducted by pharmaceutical manufacturers is extrapolated from these trials and applied to the population, although the majority of trials are conducted on healthy, young sample groups. Doses in trials are often high as manufacturers need to prove their drug is effective, as opposed to finding the lowest possible therapeutic dose. (23) It may be tempting to omit or manipulate data that could negatively affect trial results; this may not become apparent until after drug approval, adversely affecting patients.

An example concerns the risk of suicidality in adolescents taking selective serotonin reuptake inhibitor (SSRI) antidepressants, such as fluoxetine and paroxetine, coming to light years after drug approval. Aggressive behaviour, restlessness and increased hostility

in children and adolescents were described, with some reports showing cases of violence and murder. (28) For paroxetine in particular, drug companies retrospectively noted that for adults of all ages with depression, the frequency of suicidal behaviour was higher in patients (0.32%) compared to those treated with placebo (0.05%). (29)

There was a noticeable discrepancy between published and unpublished trials, which was shown in a 2004 UK review using Medicine and Healthcare products Regulatory Agency data. Under-reporting of this side effect was found to be due to limitation in the design of clinical trials, such as response-based selection bias and insufficient lead-in periods. (28) Therefore, it is important to be wary of published trial information, with clinical study reports being far more reliable in determining the risk of serious harm in prescribed medications.

R&D costs are estimated by industry-funded studies at £1.15 billion per drug. (30) It is difficult to ascertain whether drug prices are justified or whether they are a result of pharmaceutical greed. Scannell et al. (31) attributes the high production cost to a decline in R&D efficiency, possibly due to overcautious regulation of the industry. It was noted that trials often fail early due to the absence of a drug's positive effect in trials of low patient numbers, therefore increasing costs in the long term. Pharmaceutical financial motive may therefore negatively influence the medical profession.

The future

The medical profession relies on the pharmaceutical industry; instead of fighting against commercialism, working together may be a solution to the issues faced. This could be carried out through transparency in research and clinical endeavours. It may be more applicable to influence demand for pharmaceuticals via prescribing doctors. (32) The industry could work with hospital consultants and GPs to identify medication demand. Patients do not have the power to obtain drugs themselves without a prescription. Giving control back to the doctor through identifying prescribing needs in their experience and feeding this back to drug companies could be a solution. This will empower the profession, while still ensuring manufacturers have products to sell, as medication does of course play a key role in healthcare provision.

Further regulation of the pharmaceutical industry globally would improve efficiency and availability of life-changing medication to all populations. Improving productivity would drive down cost prices and enable the future viability of the healthcare system. (31) More realistic government funding to the pharmaceutical industry to match the increase in production costs for pharmaceutics would relieve financial pressures on manufacturers. Furthermore, independently funded and transparent research could be carried out to ensure patient safety. (23)

Conclusion

As a student entering the profession, it is important to be aware of the changing

nature of what it means to be a medical professional in society. This ultimately means acknowledging that the profession is dynamic, influenced by market forces and governed in a way that influences clinical practice. Considering public perception of medication, as well as their view of professionals, is imperative in making decisions on clinical practice. The pharmaceutical industry does have the power to influence the medical profession, however doctors still have overriding responsibility and a duty of care on medication prescribed to their patients.

References

1. Palmer B, Wong A. and Singla M. Hearing the voice of medical students worldwide. PLoS Med. 2005;2(4):99.

https://doi.org/10.1371/journal.pmed.0020099

PMid:15839741 PMCid:PMC1087213

2. Kaba R and Sooriakumaran P. The evolution of the doctor-patient relationship. Int J Surg. 2007;5(1):57-65.

https://doi.org/10.1016/j.ijsu.2006.01.005

PMid:17386916

3. Broom A. Medical specialists' accounts of the impact of the internet on the doctor/patient relationship, Health (London). 2005;9:319-338.

https://doi.org/10.1177/1363459305052903

PMid:15937035

4. Haug MR. Deprofessionalization: an alternate hypothesis for the future. Sociol Rev Monogr.1973;20:195.

https://doi.org/10.1111/j.1467-954X.1972.tb03217.x

5. Rose N. Beyond medicalisation. Lancet. 2007;369:700-702.

https://doi.org/10.1016/S0140-6736(07)60319-5

6. Bloor K and Freemantle N. Fortnightly Review: Lessons from international experience in controlling pharmaceutical expenditure II: influencing doctors. BMJ. 1996:312:1525-1527

https://doi.org/10.1136/bmj.312.7045.1525

PMid:8646148 PMCid:PMC2351250

7. Hawkes N. NICE sets cap on drugs costing more than £20m. BMJ. 3027;356:1372.

https://doi.org/10.1136/bmj.j1372

PMid:28314710

8. Baines D, Brigham P, Phillips D, Tolley K and Whynes D. GP fundholding and prescribing in UK general practice. Public Health. 1997;111:321-325.

https://doi.org/10.1038/sj.ph.1900377

PMid:9308382

9. Raftery J. Value based pricing: can it work? BMJ. 2013; 347.

https://doi.org/10.1136/bmj.f5941

PMid:24124158

10. NICE. Technology appraisal guidance. London. 2017 [accessed 18 Nov 2017]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance.

11. NICE. Developing and updating local formularies.London. 2014 [accessed 18 Nov 2017]. Available from: https://www.nice.org.uk/guidance/mpg1.

12. WHO. Technology appraisal programme of the National Institute for Clinical Excellence. Geneva: WHO. 2003 [accessed 18 Nov 2017]. Available from: https://apps.who.int/iris/handle/10665/107504.

13. Lorgelly P. The impact of Brexit on pharmaceuticals and HTA. PharmacoEconomics – Open. 2018;2(2):87-91.

https://doi.org/10.1007/s41669-018-0072-5

PMid:29557537 PMCid:PMC5972122

14. Kmietowicz Z. NICE rejects trastuzumab emtansine for use on NHS. BMJ. 2015;351:h6837.

https://doi.org/10.1136/bmj.h6837

PMid:26673454

15. Gulland A. Cystic fibrosis drug is not cost effective, says NICE. BMJ. 2016;353:i3409.

https://doi.org/10.1136/bmj.i3409

PMid:27325384

16. Wise J. MPs call for fresh talks to end deadlock over cystic fibrosis drug. BMJ. 2018;360:k1337.

https://doi.org/10.1136/bmj.k1337

PMid:29563081

17. Williams S, Gabe J and Davis P. The sociology of pharmaceuticals: progress and prospects, Sociol of Health & Illn, 2008;30(6):813-824.

https://doi.org/10.1111/j.1467-9566.2008.01123.x

PMid:18761505

18. NHS Digital. Prescriptions dispensed in the community, statistics for England - 2006-2016 [PAS] - NHS Digital. 2018 [Accessed 24 Jun 2018]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/prescriptions-dispensed-in-the-community/prescriptions-dispensed-in-the-community-statistics-for-england-

2006-2016-pas.

19. Dowden A. The expanding role of nurse prescribers. Prescriber. 2016;27(6):24-27.

https://doi.org/10.1002/psb.1469

20. Colgrove J. The McKeown thesis: A historical controversy and its enduring influence. Am J of Public Health. 2002;92(5):725-729.

https://doi.org/10.2105/AJPH.92.5.725

PMid:11988435

21. Timmermans S and Kolker E. Evidence-based medicine and the reconfiguration of medical knowledge. J Health Soc Behav. 2004;45:177–193.

22. Light D and Levine S. The changing character of the medical profession: a theoretical overview. Milbank Q. 1988;66:10.

https://doi.org/10.2307/3349912

PMid:3075008

23. Busfield J. Pills, power, people: sociological understandings of the pharmaceutical industry, Sociology. 2006;40:297-314.

https://doi.org/10.1177/0038038506062034

24. Sharma T, Guski L, Freund N. and Gøtzsche P. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ. 2016;352:i65.

https://doi.org/10.1136/bmj.i65

PMid:26819231 PMCid:PMC4729837

25. Propper C. The demand for private health care in the UK. J Health Econ. 2000;19:855-876.

https://doi.org/10.1016/S0167-6296(00)00045-X

26. Mehr S and Brook R. Factors influencing the economics of biosimilars in the US. J Med Econ. 2017;20:1268-1271.

https://doi.org/10.1080/13696998.2017.1366325

PMid:28796564

27. Silverstein M, Loftus E, Sandborn W, Tremaine W, Feagan B, Nietert PJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology. 1999:117:49-57.

https://doi.org/10.1016/S0016-5085(99)70549-4

28. Pécoul B, Chirac P, Trouiller P and Pinel J. Access to essential drugs in poor countries a lost battle? JAMA. 1999;281(4):361–367.

https://doi.org/10.1001/jama.281.4.361

PMid:9929090

29. GlaxoSmithKline. Important prescribing information. Letter to healthcare professionals. May 2006 [accessed 24 June 2018]. Available from: www.gsk.com/media/388699/adult_hcp_letter.pdf.

30. Cancer Research UK. 'Health economics: the cancer drugs cost conundrum'. Cancer Research UK website. 2016 (accessed 24 Jun 2018). Available from: www.cancerresearchuk.org/funding-for-researchers/ research-features/2016-08-10-health-economics-the-cancer-drugs-cost-conundrum.

31. Scannell J, Blanckley A, Boldon H and Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov. 2012;11(3):191-200.

https://doi.org/10.1038/nrd3681

PMid:22378269

32. Golder S, Loke Y, Wright K and Norman G. Reporting of adverse events in published and unpublished studies of health care interventions: a systematic review. PLos Med. 2016;13(9):e1002127.

https://doi.org/10.1371/journal.pmed.1002127

PMid:27649528 PMCid:PMC5029817

The British Student Doctor, 2019;3(2):19-26
doi: 10.18573/bsdj.49
Discussion

Legal solutions to medical problems: understanding ownership of bodily property and end-of-life issues using a rights terminology

DISCUSSION

AUTHORS

Saloni Patel
University of Oxford

Address for Correspondence:

Saloni Patel
Jesus College
Turl Street
Oxford
OX1 3DU

Email: spatel08@hotmail.co.uk

No conflicts of interest to declare

Accepted for publication: 23.03.19

ABSTRACT

Summary:

This essay takes two contentious issues of contemporary society – end-of-life and ownership of bodily material and examines them through a legal lens.

Relevance:

In today's litigation culture, the spheres of medicine and law increasingly overlap, sparking a need to leave the dichotomies behind and explore the symbiosis between these fields.

Take Home Messages:

On the basis of (1) consistency, (2) coherency and (3) control, it is argued that a rights terminology would helpfully organise the way we approach medical decision-making in these two contexts.

From Ethics to the Law

In the field of medical law wherein ethical and legal issues jostle against each other, a rights terminology can prove a valuable mechanism in balancing both legal and ethical concerns. Inherent in the notion of rights is acknowledgement of ethical issues, such as equal worth and dignity, and integral to the application of rights are legal duties. Therefore, a rights-based approach has the advantage of engaging, albeit not resolving, this insistent conflict between ethics and the law.

There are three components to a rights-based approach: the subject holder, the object (the person against whom the right is held), and the content. The content of the right provides the substantive basis for the right, grounding the approach in a clear ethical principle. The subject holder and object exist in a correlative relationship with each other as the object holds a duty to the subject holder. This relationship structure of rights and duties sets up a clear response mechanism, spurring definitive action if rights are to be upheld. Whilst other ethical approaches may have the advantage of nuance and subtlety, they can prove too vague to be practically useful. These alternative approaches include utilitarianism, the ethics of care and deontology. According to utilitarianism, we should choose the course of action that has the best overall consequences for everyone concerned. Yet, with this we encounter the impossible matter of defining '*good*'. The ethics of care approach is focussed on care and empathy, but it prioritises these above choices and does not account for the fact that we all think and feel differently. Deontology is a rule-orientated theory and decisions are governed by whatever the rule demands, irrespective of the consequence of an action. This has the disadvantage of treating people as ends rather than means and can therefore be seen as a blunt tool for decision-making in this area.

Bodily Material and End of Life

This essay advocates for a rights-based approach in two specific contexts: bodily material and end-of-life. For the purpose of this essay, human bodily material is defined as any material which consists of or includes human cells, other than hair or nail from the body of a living person. The Human Tissue Act 2004 is the main guidance for the law in this area.

Euthanasia or assisted dying is the act of deliberately ending a person's life to relieve suffering. This includes a range of actions which are sometimes separated into '*active*' and '*passive*'. Active euthanasia refers to deliberate intervention to end someone's life by, for example, the administration of large doses of drugs that are not otherwise needed for treatment. Passive euthanasia refers to the withholding or withdrawing of treatment that is needed to maintain life. Whilst both active and passive euthanasia are illegal under English law, this distinction is often used in the theoretical discourse on end-of-life and sometimes seems to slip into judicial reasoning. Moreover, withdrawing life-sustaining treatment if this is in the person's best interests can be part of palliative care and is not considered euthanasia, but this is a tricky line to draw. Suicide is not a criminal act and refusal of treatment is permitted – even if it would result in death – so long as the decision is voluntary and informed, and the patient has

the requisite capacity.

Consistency and Coherency

Significant inconsistencies can be identified in the bodies of law pertaining to both end-of-life and ownership of bodily material; a rights-based approach would aid reconciliation between the conflicting legal and ethical issues at play in these contexts.

The first controversy is the active-passive distinction which is used to rationalise withdrawal of life-sustaining treatment as an omission rather than an action. An omission is a failure to act and in other legal contexts attracts different legal consequences from positive conduct. This "*semantic sleight of hand*" allows a distinction to be made between '*killing*' and '*letting die*'; the latter undoubtedly holds more intuitive appeal; however this distinction is logically incoherent. (1) In stopping treatment, a positive act still takes place. For example, in the case of Airedale NHS Trust v Bland the patient only passed away because "*a hand grasped the naso-gastric tube and pulled it out*". (2) Driving this linguistic artifice appears to be the "*moral bias*" that it is wrong to kill. (3) Whilst this is undoubtedly true in a general sense, the unnecessary commitment to it in refusal of treatment, wherein the individual seeks death, has forced the judiciary to reason creatively to avoid the conclusion that doctors are murderers. (4) However, flipping this bias to positively recognise a right-to-die would eradicate the reprehensibility associated with these actions, and thus the need to defend them. Consequently, the need for this legal fiction dissolves, restoring coherency in the law.

In the case of Bland (5) a patient refused treatment and the courts used the act-omission distinction to rationalise why the doctors were not guilty of murder. However, as academic Foster has noted, "*the language of duty is more satisfactory*". (2) A right demands a correlative duty and by recognising a right-to-die, the result in this case could have been straightforwardly justified as the doctor having a resultant duty not to continue feeding.

Additionally, the law makes an incoherent distinction between lawful and unlawful life-shortening practices. Dying from starvation or suffocation (means of death permitted through refusal of treatment) can often be more protracted and distressing than the quick and painless death that would be induced by a single fatal injection that is currently prohibited. The arbitrary nature of this distinction was highlighted in the Nicklinson case. (6) After locked-in syndrome left Mr. Nicklinson unable to speak or move, he argued that the current prohibition on assisted dying is a breach of human rights because it fails to recognise his right-to-die. If a man such as Mr. Nicklinson has the right to starvation, leading to a long and painful death, surely, he should also have the right to a quick and painless death? Using and recognising rights would eliminate this discrimination between lawful and unlawful life-shortening practices, giving the law more coherency.

Moreover, there is currently disparity between offence (unlawful action) and punishment (legal consequence), giving unsatisfactory uncertainty to the law. A rights-based approach could better manage this. Despite their widely publicised illegality, assisted dying prosecutions are rare, and convictions are rarer still. As leading academic

McLean asks, "*what purpose is served by a law which technically criminalises behaviour which it then effectively ignores and forgives?*"; this does not accord with constitutional principle. (7) Contrary to academic Greasley's remarks that the "*pre-Purdy approach of wilful blindness was the best method of navigating the tricky moral territory of assisted suicide*", certainty in this area of the law is something we should be striving towards. (8) Why settle for '*wilful blindness*' when recognition of a right could give the judiciary a concrete tool on which to base end-of-life decisions? Working on a backdrop of fierce emotion, investment of certainty and coherence into the law is of the upmost importance. Clarification of policy is a step forward, but recognition of a right-to-die would standardise decision-making even further.

In the area of bodily material too, a rights-based approach would offer coherency and consistency with regard to legal consequence. Failing to recognise property rights of human bodily material significantly limits the remedies that can be sought when legal disputes arise. For example, in a Californian case, a doctor used embryos without consent. Given the reluctance to recognise embryos as property, the doctor could not be charged with theft as this is a property offence. Instead, the doctor in question was charged with mail fraud, an incongruous remedy that failed to correct the alleged harm. (9) In contrast, the case of Yearworth has proven the merit of recognising property rights. (10) In this case a remedy based on bailment was allowed where it would have been otherwise inaccessible. Whilst this was promising, the development should be taken further and extended into a comprehensive property regime. As the academic Moses has noted, "*legal categories such as property… create default rules that can be applied in diverse contexts*". (11) Therefore, rather than the default being the '*no property*' rule and forms of property rights being identified on an ad-hoc basis, the best way forward would be a rights-based approach that recognises property rights as the default.

Control

The appeal of using property rights is the strong degree of control it gives to the individual, comparable with the strong emphasis put on the protection of bodily autonomy in other areas of medical law. Property rules create an institutional structure that permits the owner to function as the supreme agenda setter for the resource. (12)

The case of Moore is a useful example of how a rights-based approach could give better effect to bodily autonomy. (13) In this case a doctor used human tissue, removed from the patient in the course of treatment, to make a '*cell line*' which was then patented for commercial use. It was ruled that a prosecution based on property rights could not be brought. In his dissent Justice Mosk made the pertinent point that the law should at least recognise Moore's right to do with his own tissue whatever the third-parties did with it. (14) The failure to recognise property rights meant that "*the person who made 'everything possible' was left with nothing*". (14) A rights-based approach could alleviate this ethical injustice by allocating the originator of this bodily material as the first owner, allowing them to share in the products and profits of their material. Further, it would mean that any subsequent transfer would have to be implemented validly, necessitating clarity as to what legally occurs when this type of material is transferred. Of course, the argument against this is that it imposes more onerous duties on third-parties, such as the procurement of valid consent, which could inhibit

medical progress. However, despite this, the stability that a rights-based approach provides sustains the case for it.

Another counter-argument to a rights-based approach is that this privileges individual control to the detriment of altruistic giving. It can be rebutted however, that if people are swayed against donation this was not true altruism in the first place. Moreover, using the language of gifting as the preferred way to conceptualise transfer of bodily material is technically incoherent without acknowledgement of rights. (15) As a matter of legal principle, gifting involves the exercise of property rights. (16) "*You must have a right to possess something to give someone else the right to…it*", and therefore a property model is not in conflict with altruistic giving, but rather facilitates it. (17) Therefore, communal interests could still be realised using gifts and charitable trusts, whereby multiple researchers can use the tissue at the same time.

Similarly, legal recognition of a right-to-die would protect control in this sensitive area. Often, the patient seeking death will have lost control of significant aspects of their life but assisted death provides an assurance that they can control these last moments in a private and peaceful manner. This is exemplified in a study conducted in Washington and Oregon wherein 90% and 89% of patients respectively, cited the decreasing ability to participate in activities that made life enjoyable as a principal reason for requesting physician-assisted suicide. (18) Control over death gives more control during life and as recognised in Lord Hope's dictum in Purdy: "*the way [one chooses] to pass the dying moments of one's life is part of the act of living, and she has a right to ask that this be accepted*". (19) In particular, using a rights-based approach better protects dignity; there is a right not to be "*forced to linger on in old age or in states of advanced physical or mental decrepitude which conflict with strongly held ideas of self and personal identity*". (19) These last few days of life are precious and people should be liberated from fear by the confidence of control. A rights-based approach affords this control, empowering the patient, at a time when they are at their most vulnerable.

Changes in attitude

In the interests of balance, some of the arguments against the recognition of rights should be considered. There is a forceful concern that accepting a right to die would result in widespread attitude changes, coarsening the way we think about life and death – a slippery slope. (20) Greasley warns that symbolic statements are sent to disabled people when assisted death is permitted and that this leads to a change in how they, and those around them, view their condition and their options. (21) However, the argument regarding signals and messages can run the other way; by failing to recognise a right to die we may also be sending a signal that those who wish for death are weak or ungrateful. It is wrong for us to impose a judgement on the worthiness of another's life (even if it is a positive one). In an article for the Medical Law Review, Ford advanced the '*person paradox*' argument against a right to die. According to this, an entity which is rational and autonomous is unreasonable in wishing for its own demise, since in wishing for this it is wishing for the destruction of something of "*ultimate value*". (22) However, as academic Harris riposted, "*if the most significant interest is that life will end*

when the person whose life it is wants it to then there is no paradox", and in discussing attitude change to life and death this is the key. (23) Failing to recognise a right to die separates the person from the life in question and arguably this does the greatest violence to our understandings of life and death.

Moreover, we can be too quick to categorise people as vulnerable. Viewing them as easily coerced or incompetent is patronising and fails to respect their agency and autonomy over their lives. As Harris argues, whilst persons should have the value of their lives respected, they are not "*doomed to have it respected. They can waive their right*". (22) Properly understood, a rights-approach provides individuals with options; they may choose to exercise a right if it is important to them, but there is no imposition to do so. In our society which champions liberty and seeks to promote freedom of action, a rights-based approach seems the only way forward.

In the purview of ownership over bodily material, there is the concern that a rights-based approach introduces a market rhetoric that distastefully objectifies and commoditises people. (24) As to the objectification concern, this attitude is already present. Human biomaterials are things which are controlled, transferred and used so applying property principles "*does not alter how we treat them, but instead gives legal protection to what we already do*". (17) Moreover, allowing matter to be the subject of property is not synonymous with making it subject to free trade; there are many examples of restrictions on the sale of things which are property, such as firearms or drugs. (15) Inappropriate use can always be limited by statute and the Human Tissue Act 2004 is an existing example of how the law can legislate against exploitation to assuage these concerns.

It has also been argued that property rights are inappropriate for protecting the spiritual values that are bound in human biomaterial. (25) However, property rules are used to protect scarce resources that have value and, as Douglas has argued, it is the very specialness of bodily material which makes it suited to being treated as property. (25) Therefore, rather than damaging personhood, the property approach engages with it.

A rights-based approach gives decision-making consistency and coherency (legal concerns) and affords individuals control, protecting their autonomy and dignity (ethical concerns). By effectively reconciling both legal and ethical issues in this way, a rights terminology is a helpful approach.

Without a recognition of rights, the law will remain forced to invent moral and legal fictions, and make arbitrary distinctions, to avoid unjust results. Despite the ethical impasses, the law must be clear and intelligible, allowing citizens to be knowable, and a rights-based approach does this. The Royal College of Physicians recently adopted a neutral stance on the subject of assisted dying, reflecting the range of members' opposing views as well as growing support for a change in the law (26). Discussion of the law surrounding assisted dying is likely to continue and medical students and junior doctors should engage plainly in the discourse that follows. It is much more

intrusive to block an action than allow an action to be available, which people can be free not to choose.

References

1. Kennedy I. Treat Me Right: Essays in Medical Law and Ethics. Oxford: Clarendon Press, 1998. p351.

2. Foster C. Airedale NHS Trust v Bland [1993]. In: Herring J and Wall J, editors. Landmark Cases in Medical Law. Oxford: Hart; 2015.

3. Miller F, Truog R, and Brock D. Moral Fictions and Medical Ethics. Bioethics. 2010;24(9):453.

https://doi.org/10.1111/j.1467-8519.2009.01738.x

PMid:19594726

4. McGee A. Does withdrawing life-sustaining treatment cause death or allow the patient to die? Medical Law Review. 2014;22:26.

https://doi.org/10.1093/medlaw/fwt034

PMid:24421396

5. Airedale NHS Trust v Bland [1993] AC 789.

6. R (Nicklinson) v Ministry of Justice [2014] UKSC 38.

7. McLean S. Assisted Dying: Reflections on the Need for Law Reform. Abingdon: Routledge-Cavendish; 2007. p.144.

8. Greasley K. R (Purdy) v DPP and the case for Wilful blindness. Oxford Journal of Legal Studies. 2010:326.

https://doi.org/10.1093/ojls/gqq010

9. McDonald J, Christensen K. No Jail: Fertility Doctor Gets Home Detention, Fine. Anaheim: Orange County Register. 1998.

10. Yearworth v North Bristol NHS Trust [2009] EWCA Civ 37.

11. Moses L. The problem with alternatives: The importance of property law in regulating excised human tissue and in vitro embroys. In: Goold I, Herring J, Skene L, and Greasley K, editors. Persons, Parts and Property: How Should We Regulate Human Tissue in the 21st Century? Oxford: Hart Publishing; 2014. p201.

12. Katz L. Exclusion and Exclusivity in Property Law. The University of Toronto Law Journal. 2008;58(3):275.

https://doi.org/10.3138/utlj.58.3.275

13. Moore v Regents of the University of California and Ors (1990) 51 Cal 3d 120.

14. Herring J, Chau PL. My Body, Your Body and Our Bodies. Medical Law Review. 2007;34:53.

https://doi.org/10.1093/medlaw/fwl016

PMid:17200155

15. Donaldson Committee. Stem Cell Research – Medical Progress with Responsibility. Department of Health; 2000 [accessed 10 Mar 2017]. Available from: www.doh.gov.uk/cegc/.

16. Goold I, Quigley M. Human Biomaterials: The Case for a Property Approach. In: Goold I, Herring J, Skene L and Greasley K, editors. Persons, Parts and Property: How Should We Regulate Human Tissue in the 21st Century? Oxford: Hart Publishing; 2014.

17. Oregon Department of Human Services. Fourteenth Annual Report on Oregon's Death with Dignity Act 2011. Oregon: Oregon Department of Human Services; 2011 [accessed 1 Mar 2017]. Available from: http://public.health.oregon.gov/ProviderPartnerResources/EvaluationReseaarch/DeathwithDIgnityAct/Documents/year14.pdf.

18. R (Purdy) v DPP [2009] UKHL 45

19. Keown J, Jackson E. Debating Euthanasia. Oxford: Hart; 2012.

20. Greasley K. R (Purdy) v DPP and the case for Wilful blindness. Oxford Journal of Legal Studies. 2010:319.

https://doi.org/10.1093/ojls/gqq010

21. Ford M. The Person Paradox and the Right to Die. Medical Law Review. 2005;13:94.

https://doi.org/10.1093/medlaw/fwi004

22. Harris J. The Right to Die Lives: There is no Personhood Paradox. Medical Law Review. 2005;13:392.

https://doi.org/10.1093/medlaw/fwi030

23. Skene L. Arguments Against People Legally "Owning" Their Own Bodies, Body Parts and Tissue. Macquarie Law Journal. 2002;2:165.

24. Rao R. Property, Privacy, and the Human Body. Buffalo University Law Review. 2000;80:359.

25. Douglas S. Property Rights in Human Biological Material. In: Goold I, Herring J, Skene L and Greasley K, editors. Persons, Parts and Property: How Should We Regulate Human Tissue in the 21st Century? Oxford: Hart Publishing. 2014. p89.

26. Royal College of Physicians. 'No majority view on assisted dying moves RCP position to neutral'. London: Royal College of Physicians; 2019 [accessed 7 June 2019]. Available from: https://www.rcplondon.ac.uk/news/no-majority-view-assisted-dying-moves-rcp-position-neutral.

The British Student Doctor, 2019;3(2):27-33
doi: 10.18573/bsdj.90
Education

Consequences of foetal and neonatal cannabis exposure

EDUCATION

AUTHOR

Sarra Alexia Griti
University of St. Andrews
School of Medicine

Address for Correspondence:

Sarra Alexia Griti
University of St. Andrews
School of Medicine
North Haugh
St. Andrews
KY16 9TF

Email: sag8@st-andrews.ac.uk

ORCID ID: https://orcid.org/0000-0002-7786-8487

No conflicts of interest to declare

Accepted for publication: 26.05.2019

ABSTRACT

Summary:

The increasing social and legal acceptance of cannabis around the world is driven by a growing body of research that points to several medical benefits, however, there remain significant risks to certain members of the population. More specifically, the maternal use of cannabis during pregnancy is associated with several adverse foetal and neonatal health consequences. While the volume of evidence is mixed, infants from women who used cannabis during pregnancy were more likely to be anaemic, have decreased birth weight and be placed in neonatal intensive care compared to infants whose mothers did not use cannabis. Findings from human and animal trials suggest that tetrahydrocannabinol (THC) and cannabidiol (CBD) may be the key chemicals responsible for many of the abnormal neurodevelopment issues such as long-term impairment in cognitive function resulting from structural alterations in synaptic plasticity. There is limited information available in the literature around the assessment of safe threshold limits, the effects of cannabis exclusive of other drugs and the long-term outcomes in the offspring. As the popularity of cannabis increases, it is important that these data gaps be addressed to provide proper guidance to women and their health care team during pregnancy.

Relevance:

The societal trend towards cannabis use raises the probability that medical students and practicing physicians will encounter pregnant women using cannabis in some form. Understanding the potential risks of maternal cannabis exposure on foetal development and pregnancy outcomes provides the knowledge required to share appropriate information and guidance with female patients during preconception, pregnancy and lactation. This in turn allows for the implementation of more comprehensive optimum wellness plans for the mother and child.

Take Home Messages:

As societies and lawmakers around the world increasingly accept the use of cannabis, it's important that medical professionals have a basic knowledge of the possible risks posed to certain vulnerable members of the population. This article provides a step in that direction.

Cannabis is a flowering plant that generally includes three species - sativa, indica, and ruderalis. The flowering buds of the female plant have high concentrations of trichomes, which are resin-filled glands containing a rich source of pharmacologically active cannabinoid compounds. The most active of these are tetrahydrocannabinol (THC) and cannabidiol (CBD), which are known for their psychoactive and non-psychoactive effects respectively. (1) As a recreational drug cannabis has for generations been used to alter sensory perception and cause elation and euphoria. This is most vividly described by the 19th century French poet Charles Baudelaire in his book Les Paradis Artificiels. (2) Most recently, research has pointed to several medical benefits including the relief of neuropathic pain. (3)

Although cannabis is still an illicit substance in most parts of the world there is growing social and legislative acceptance for its use for medical and recreational use. (4) It is the most commonly used illicit drug among women of childbearing age in developed countries, and while estimates vary, one study by Ko et al. estimates that more than 10% of pregnant women use cannabis – in fact, pregnant women who were smokers of tobacco, and used illicit drugs and alcohol were 2-3 times more likely to use cannabis. (5) Typically, cannabis is used during the first trimester as a treatment for nausea and morning sickness. (6) The legalization and commercialization of cannabis is expected to attract for-profit corporations and could result in aggressive marketing to encourage demand, similar to practices implemented by the tobacco industry. (7) For example, according to the National Survey on Drug Use and Health the use of cannabis among pregnant women in the United States has increased by 62% between 2002 and 2014. According to the study, 3.85% of pregnant women in 2014 reported cannabis use in the previous month compared with only 2.37% of pregnant women in 2002. (8, 9) Another population survey reported that pregnant users of cannabis were younger, had a lower level of education and a lower household income. (10) While it appears that the use of cannabis is growing, there continues to be a paucity of reliable evidence available regarding the use and frequency of cannabis use during pregnancy.

Impact of Cannabis Use on Foetal and Neonatal Mechanisms

As part of the human endocannabinoid system there are specific cannabinoid receptors in the body acted on by cannabinoids that affect the homeostasis of biological functions. The cannabinoid receptors are widely distributed throughout the central nervous system and the peripheral nervous system. Their greatest concentration is around the hippocampus, cortex, olfactory areas, basal ganglia, cerebellum and spinal cord, which accounts for the effects of cannabinoids on memory, emotion, cognition and movement. (11) In the foetal human brain cannabinoid receptors were detectable at 14 weeks gestation, however the receptor levels were very low throughout the second trimester. (12) The region showing a receptor density close to that seen in adults was the globus pallidus. (12) Cannabinoids can cross the placental barrier and be secreted into maternal milk to affect the expression of key genes for neural development. (13) Cannabinoid receptors are expressed in white matter and cell proliferative regions and are integral to critical neurodevelopmental events, such as neuronal proliferation, migration, and synaptogenesis. (14) Endogenous endocannabinoids also play a key role in regulating neural progenitor cell commitment and survival. (15) Thus, exposure to exogenous cannabis during pregnancy has the potential to induce supra-physiological stimulation of the endogenous cannabinoid system, which may disrupt the ontogeny of endogenous endocannabinoid signalling, and interfere with synaptogenesis and the development of neuronal interconnections. (16)

Embryonic and foetal life represents a crucial period of development involving the greatest number of cell divisions. An aspect of the impact of cannabis that has not been studied in detail involves the effects on developing organs as they progress through key stages of growth - cellular hyperplasia, non-committal cellular hyperplasia, and hypertrophy. (17) Due to the lipophilic nature of cannabis, the active ingredient THC can readily cross many types of cell barriers including the placental barrier and can directly affect the foetus. (18) An unfavourable intrauterine environment could leave the foetus vulnerable to structural and functional anomalies that can have life-long consequences. A 1988 study by Wu et al. also associated marijuana smoking to a nearly fivefold greater increment in the blood carboxyhaemoglobin level, and a near threefold increase in the amount of tar inhaled, compared to tobacco smoking. (19) This study was limited to male subjects and further study would be required to confirm whether these pulmonary hazards would also adversely impact pregnant women.

Various human and non-human studies confirm the transfer of THC across the placenta. A study by Fisher et al. indicates that THC will cross the placenta to reach a concentration equal to or higher than that of the maternal circulation. It also indicates that THC has the potential to be placento-toxic as it accumulates in the placenta and could interfere with the transfer of essential amino acids and other macromolecular precursors. (20) In another study, researchers injected THC into late-term (gestational days 146-151) rhesus monkeys to measure its placental transfer to the foetus. After analyzing for THC and 11-nor-9-carboxy-THC (11-nor), a major metabolite, they observed that maternal and foetal plasma THC levels were equal at 37ng/ml after 3 hours. However, less than 5ng/ml of 11-nor was detected in foetal plasma, with none

being detected in the placenta, foetal liver, or foetal brain. This data supports that THC rapidly diffuses through the placenta, entering the foetus. It also suggests that 11-nor does not travel through the placenta because the foetus does not readily metabolise THC into 11-nor at this late developmental stage. (21) Furthermore, from a study of the human endocannabinoid system there is evidence that THC affects trophoblast proliferation, apoptosis, differentiation, and function. (22) A study by Costa et al. found that THC impaired cytotrophoblast differentiation into synctiotrophoblast. This was caused by a reduction in the expression of syncytialisation biomarkers via a cannabinoid receptor-dependent mechanism. (23) Another study by Almada et al. found that the use of synthetic cannabinoids, such as WIN-55,212, induced cell cycle arrest through the activation of CB1 receptors. Specifically, they determined that this apoptosis was associated with a mitochondrial membrane potential disruption and the activation of caspase proteins without reactive oxygen species or recruitment of the endoplasmic reticulum stress marker CHOP. (24)

Because of the increased teratogenic action of THC on the proper functioning of the placenta, cannabis use during the first trimester of pregnancy may result in miscarriage and congenital malformations, while use after the first trimester would more likely cause delays in foetal growth and functional development. (25) A comprehensive Australian study which analyzed 416,834 live births over a 5-year period confirmed that 2,172 of all births that were associated with maternal cannabis use resulted in neonates with a higher level of foetal distress. (26) Compared with infants whose mothers did not use cannabis during pregnancy, in-utero exposure to cannabis usually resulted in pre-term birth requiring placement of newly born infants in neonatal intensive care units. (26, 27) A systematic review and meta-analysis by Gunn et al. which reviewed 24 case-controlled, cross-sectional and cohort studies also found similar findings. (28) Most studies reflect participants characterised by concurrent polysubstance use including tobacco and alcohol. To achieve more accurate conclusions future research is required that evaluates neonatal outcomes only from cannabis users exclusive of these confounding factors.

Weight & Growth Outcomes

Various studies reveal that high levels of THC exposure may result in adverse pregnancy outcomes including preeclampsia, pre-term birth, and low birth weight. Animal studies show that high doses of THC in pregnant mice and rats result in lower birth weight among offspring. (29) While some human studies showed a null association, others demonstrated a decrease in foetal weight when exposed to cannabis in-utero. (30) A 2009 Dutch study of 7,452 infants exposed to cannabis during pregnancy indicated that birth weight for those infants exposed to cannabis throughout pregnancy was on average 277 grams lower compared with non-exposed infants, and 156 grams lower for infants exposed to cannabis in early pregnancy only. (31) This is a significant effect as lower birth weight has also been associated with an increase in morbidity and mortality in infants. (32) A twin study has also shown that it is the smaller twin at birth that has the highest blood pressure later in life. (33) Other lasting consequences of lower birth weight may include lower IQ and academic achievement, higher rates of neurosensory impairments and chronic conditions. (34) Other studies by Day et al. and Gray et al. have reported a decrease in gestational length from exposure to cannabis in-utero. (35, 36)

Definitive conclusions from maternal cannabis studies on foetal growth and birth weight are limited due to many confounding variables across studies related to nutrition, prenatal care, multi-substance use and the duration and frequency of use involving these substances. An Australian multi-hospital study of pregnant women using cannabis indicated that over 33.5% of cannabis users were multidrug users. (37) As a result, it is difficult to separate the direct impact of cannabis relative to other substances.

There is also the issue of reluctance and accurate disclosure by study participants, driven by fear of legal consequences especially since cannabis use is illegal in many jurisdictions. For example, in a Brazilian hospital study, only 1 of 26 mothers who used cannabis during pregnancy reported their use. (38) A potential solution in future studies could be the use of more reliable laboratory assessments to determine cannabis use. This could include toxicological analysis of body specimens such as hair and urine, as self-reported cannabis use had poor correlation with corresponding urinalysis results. (39)

Neurobehavioural Outcomes

As exogenous cannabis binds to the receptors of the foetal endocannabinoid system it alters neurodevelopment by interfering with proper neural circuitry formation in the early brain. This adversely impacts the creation and movement of neurons, the outgrowth of their axons and dendrites and axonal pathfinding. This predisposes offspring to abnormalities in cognition and altered emotionality. (40)

A neonatal study by Fried and Makin examining 250 infants born to middle-class women showed that prenatal cannabis exposure was connected with increased tremors, startles and a poorer ability to adapt to visual stimuli. (41) Another Brazilian study of adolescent mothers with babies born at term found that neonates exposed

to cannabis during pregnancy required more time for testing and showed adverse reactions relative to arousal, regulation, and excitability. (38) Examining a different social class, yet another study by Coles et al. examining 107 infants born to low-income predominantly black women also showed that prenatal cannabis exposure resulted in a reduced ability of the neonate to focus and track external stimuli. (42) In contrast to these studies, a study by Dotters-Katz et al. found no adverse neonatal or childhood outcomes from foetal exposure to cannabis in neonates. (43) These discrepancies could be the result of confounding factors previously mentioned or even the use of different neurobehavioral scales and inconsistent follow-up periods to access deficits in cognitive functioning.

A study by El Marroun et al. showed that by early childhood, cannabis-exposed children, especially girls, develop more slowly in terms of visual–perceptual tasks and language skills, and demonstrate increased levels of aggression and poor attentiveness. (44) Cognitive and intellectual deficits seem to also be related to the timing and amount of in-utero exposure. Heavy use (defined as one or more cannabis cigarettes per day) during the first trimester was associated with lower verbal reasoning scores in children at 6 years of age when compared with their non-exposed peers, while second trimester use was associated with deficits of composite, short-term memory, and quantitative scores. (45)

Various longitudinal studies including the Ottawa Prenatal Prospective Study (OPPS) by P.A. Fried have also shown adverse effects of cannabis use. In the OPPS, involving an initial sample of 698 women, the effects of cannabis used during pregnancy was studied and offspring assessed repeatedly during the neonatal period. The results suggest that in the neonates, state alterations and altered visual responsiveness may be associated with in utero exposure to cannabis, however there was no association between cannabis exposure and infant development at 1 year. Beyond the absence-of-effect during early childhood, at the age of 4 and older there were increased behavioural problems and decreased performance on visual perceptual tasks. (46) Another epidemiological, developmental and clinical overview by El Marroun et al. also found that cannabis use in pregnancy poses major health concerns for developing children, however it was pointed out that findings have been inconsistent or difficult to interpret due to methodological issues. (47)

Overall, the inconsistent neurobehavioral results could be explained by differing population sizes and characteristics, varied assessment techniques, prevalence of concurrent maternal multidrug use, frequency and timing of cannabis exposure, maternal age, or even the socioeconomic and educational profile of the mother. Even the type and potency of cannabis used may have played a role as improved greenhouse technology in recent years has increased the THC potency of cannabis. (48)

Conclusion

Although the body of literature regarding the consequences of cannabis use during pregnancy is limited, foetal and neonatal exposure may have the potential to cause long-term growth, neurodevelopmental, and behavioural harm. For instance, at present there is evidence to indicate that cannabis is responsible for causing low birth weight, and the need for neonatal intensive care of newborns. In addition, the THC and CBD present in cannabis may be linked to long-term impairments in cognitive function. In 2017, because of the concerns regarding impaired neurodevelopment, the American College of Obstetricians and Gynecologists published Committee Opinion Number 722 that discourages physicians from prescribing cannabis for medicinal purposes during preconception, pregnancy, and lactation. (49)

The results of the limited number of studies are conflicting and complicated since they often reflect participants characterized by polysubstance use. There is inadequate conclusive research on the specific perinatal impacts of THC and CBD, excluding other bioactive compounds. Thus, further research is needed to isolate the effect of THC and CBD exclusive of tobacco, alcohol and other drug consumption. Future studies could also determine the neurodevelopmental effect of high-potency formulations and low-cost synthetic cannabinoids, as their effects may pose different risks to the foetus.

Given the nature of maternal polysubstance use, coupled with legislation trends that are likely to increase the use of cannabis, there is a need for more through screening and substance management for women of reproductive age. There is also a need for more focused research to comprehensively evaluate the long-term effects of prenatal cannabis exposure on foetal development and pregnancy outcomes. This will allow maternal decisions on the use of cannabis to be made on firmer scientific grounds. In the interim, because of the potential adverse foetal and neonatal health consequences, there should be increased action on the part of governments, medical associations and physicians to inform women of the potentially harmful impact of cannabis exposure use during pregnancy.

References

1. MacCallum C, Russo E. Practical Considerations in Medical Cannabis Administration and Dosing. European Journal of Internal Medicine. 2018;49:12-19.

https://doi.org/10.1016/j.ejim.2018.01.004

PMid:29307505

2. Iversen LL. The Science of Marijuana. Oxford: Oxford University Press;2000.

3. Lee G, Grovey B, Furnish T, et al.Medical Cannabis for Neuropathic Pain. Curr Pain Headache Rep. 2018;22(1):8.

https://doi.org/10.1046/j.1365-2044.2001.02269.x

PMid:11703238

4. Ingraham C. Just how Mainstream is Marijuana? There is a Congressional Cannabis Caucus. Washington DC: The Washington Post; 2016 [accessed 28 October 2018]. Available from: https://www.washingtonpost.com/news/wonk/wp/2017/02/17/just-how-mainstream-is-marijuana-theres-now-a-congressional-cannabis-caucus/?utm_term=.9dab402901c6/.

5. Ko JY, Farr SL, Tong VT, et al. Prevalence and patterns of Marijuana use among Pregnant and Nonpregnant Women of Reproductive Age. Am J Obstet Gynecol. 2015;213(2):e1–e10.

https://doi.org/10.1016/j.ajog.2015.03.021

PMid:25772211

6. Volkow N.D., Compton W.M., Wargo E.M. The Risks of Marijuana Use During Pregnancy. JAMA. 2017;317(2):129-130.

https://doi.org/10.1001/jama.2016.18612

PMid:27992628

7. Cause and effect: tobacco marketing increases youth tobacco use - findings of the 2012 Surgeon General's report. Boston: Center for Public Health and Tobacco Policy; 2012 [accessed 28 October 2018]. Available from: www.tobaccopolicycenter.org/documents/SGR%20NY%205-25-12. pdf.

8. Results from the 2016 national survey on drug use and health: detailed tables. Maryland.National Survey on Drug Use and Health;2016 [accessed 28 October 2018]. Available from:

https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf

https://doi.org/10.1001/jama.2016.17383

PMid:27992619 PMCid:PMC5595220

9. Brown, Q.L., Sarvet AL, Shmulewitz D, et al. Trends in Marijuana Use Among Pregnant and Non-Pregnant Reproductive-Aged Women, 2002-2014. Journal of the American Medical Association. 2016; 317(2).

10. Van Gelder MM, Reefhuis J, Caton AR et al. Characteristics of Pregnant Illicit Drug Users and Associations between Cannabis use and Perinatal Outcome in a Population-based Study. National Birth Defects Prevention Study. Drug Alcohol Depend. 2010; 109:243-7.

https://doi.org/10.1016/j.drugalcdep.2010.01.007

PMid:20171023

11. Kumar RN, Chambers WA, Pertwee RG. Pharmacological Actions and Therapeutic Uses of Cannabis and Cannabinoids. Anesthesia. 2001;56(11), 1059-1068.

https://doi.org/10.1046/j.1365-2044.2001.02269.x

PMid:11703238

12. Biegon A, Kerman I. Autoradiographic Study of Pre- and Postnatal Distribution of Cannabinoid Receptors in Human Brain. NeuroImage. 2001;14(6):1463-8.

https://doi.org/10.1006/nimg.2001.0939

PMid:11707102

13. Gomez M, Hernandez M, Johansson B, et al. Prenatal Cannabinoid and Gene Expression for Neural Adhesion Molecule L1 in the Fetal Brain. Brain Research: Developmental Brain Research. 2003;147(1-2), 201-207.

https://doi.org/10.1016/j.devbrainres.2003.10.016

PMid:15068010

14. Díaz-Alonso, J., Guzmán, M., Galve-Roperh, I. Endocannabinoids via CB1 receptors act as neurogenic niche cues during cortical development. Philosophical Transactions B of the Royal Society of London Biological Sciences. 2012;367(1607): 3229–3241.

https://doi.org/10.1098/rstb.2011.0385; PMid:23108542 PMCid:PMC3481527

15. Jutras-Aswad D, DiNieri JA, Harkany T, et al. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome.

Eur Arch Psychiatry Clinical Neuroscience. 2009;259: 395–412.

https://doi.org/10.1007/s00406-009-0027-z

PMid:19568685

16. Jacques SC, Kingsbury A, Henshcke P et al. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology. 2014;34: 417–424.

https://doi.org/10.1038/jp.2013.180; PMid:24457255

17. Winick M. Cellular Changes during Placental and Fetal Growth. American Journal of Obstetrics and Gynecology. 1971;109(1):166-176.

https://doi.org/10.1016/0002-9378(71)90853-2

18. Little B, VanBeveren T. Placental Transfer of Selected Substances of Abuse. Seminars in Perinatology. 1996; 20:147-153.

https://doi.org/10.1016/S0146-0005(96)80082-6

19. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. New England Journal of Medicine. 1988;318(6):347-51.

https://doi.org/10.1056/NEJM198802113180603

PMid:3340105

20. Fisher S, Atkinson M, Chang B. Effect of Δ-9-Tetrahydrocannabinol on the in Vitro Uptake of α-Amino Isobutyric Acid by Term Human Placental Slices. Pediatric Research. 1987; 21:104-107

https://doi.org/10.1203/00006450-198701000-00022

PMid:3025804

21. Bailey, J.R., Cunny, H.C., Paule, M.G., Slikker Jr., W. Fetal disposition of delta 9-

tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. Toxicology and Applied Pharmacology. 1987;90(2); 315-21.

https://doi.org/10.1016/0041-008X(87)90338-3

22. Costa MA. The endocannabinoid system: a novel player in human placentation. Reproductive Toxicology. 2016;61:58-67.

https://doi.org/10.1016/j.reprotox.2016.03.002

PMid:26965993

23. Costa MA, Fonesca BM, Marques F, Teixeira NA, Correida-da-Silva G. The psychoactive compound of Cannabis sativa, Δ(9)-tetrahydrocannabinol (THC) inhibits the human trophoblast cell turnover. Toxicology. 2015; 334:94-103.

https://doi.org/10.1016/j.tox.2015.06.005

PMid:26070387

24. Almada M, Costa L, Fonseca BM, et al. The synthetic cannabinoid WIN-55,212 induced-apoptosis in cytotrophoblasts cells by a mechanism dependent on CB1 receptor. Toxicology. 2017; 385:67-73.

https://doi.org/10.1016/j.tox.2017.04.013

PMid:28495606

25. Smith CG, Asch RH. Acute, short-term, and chronic effects of marijuana on the female primate reproductive function. National Institute on Drug Abuse. 1984;44:82-96.

26. Burns, L., Mattick, R.P., Cooke, M. The Use of Record Linkage to Examine Illicit Drug Use in Pregnancy. Addiction. 2006;101(6).

https://doi.org/10.1111/j.1360-0443.2006.01444.x

PMid:16696631

27. Hayatbakhsh MR, Flenady VJ, Gibbons KS, et al. Birth outcomes associated with cannabis use before and during pregnancy. Pediatric Research. 2012;71:215–19.

https://doi.org/10.1038/pr.2011.25

PMid:22258135

28. Gunn JKL, Rosales CB, Center KE, Nunez A, et al. Prenatal Exposure to Cannabis and Maternal and Child Health Outcomes: a systematic Review and Meta-analysis. BMJ Open. 2016.

https://doi.org/10.1136/bmjopen-2015-009986

PMid:27048634 PMCid:PMC4823436

29. Fried PA. Short and long-term effects of pre-natal cannabis inhalation upon rat offspring. Psychopharmacology (Berl). 1976;50:285-91.

https://doi.org/10.1007/BF00426846

30. Linn, S., Schoenbaum, S.C., Monson, R.R., Rosner, R., Stubblefield, P.C., Ryan, K.J. The association of marijuana use with outcome of pregnancy. Am J Public Health. 1983; 73:1161–1164.

https://doi.org/10.2105/AJPH.73.10.1161

PMid:6604464 PMCid:PMC1651077

31. El Marroun H, Tiemeier H, Steegers EA, et al. Intrauterine cannabis exposure affects fetal growth trajectories: The Generation R Study. Journal of the American Academy of Child & Adolescent Psychiatry. 2009; 48:1173–81.

https://doi.org/10.1097/CHI.0b013e3181bfa8ee

PMid:19858757

32. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. New England Journal of Medicine. 1985;312:82–90.

https://doi.org/10.1056/NEJM198501103120204

PMid:3880598

33. Levine RS, Hennekens CH, Jess MJ. Blood pressure in prospective population-based cohort of newborn and infant twins. British Medical Journal. 1994;308(6924):298-302.

https://doi.org/10.1136/bmj.308.6924.298

PMid:8124117 PMCid:PMC2539292

34. Hack M, Flannery DJ, Schluchter M, et al. Outcomes in young adulthood for very-low-birth-weight infants. New England Journal of Medicine. 2002;346:149–57.

https://doi.org/10.1056/NEJMoa010856

PMid:11796848

35. Day N, Sambamoorthi U, Taylor P, et al. Prenatal marijuana use and neonatal outcome. Neurotoxicology & Teratology. 1991;13(3):329-34.

https://doi.org/10.1016/0892-0362(91)90079-C

36. Gray TR, Eiden RD, Leonard KE, et al. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. Clin Chem. 2010;56:1442-50.

https://doi.org/10.1373/clinchem.2010.147876

PMid:20628142 PMCid:PMC3163087

37. Quinlivan, J. A. and Evans, S. F. The impact of continuing illegal drug use on teenage pregnancy outcomes—a prospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2002;109:1148–1153.

https://doi.org/10.1016/S1470-0328(02)01936-5

https://doi.org/10.1111/j.1471-0528.2002.01536.x

PMid:12387469

38. De Moraes Barros MC, Guinsburg R, De Araújo Peres C, et al. Exposure to Marijuana During Pregnancy Alters Neurobehavior in the Early Neonatal Period. The Journal of Pediatrics. 2006;149(6):781-787.

https://doi.org/10.1016/j.jpeds.2006.08.046

PMid:17137892

39. Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. New England Journal of Medicine. 1989;320:762–8.

https://doi.org/10.1056/NEJM198903233201203

PMid:2784193

40. Richardson K, Hester A, McLemore G. Prenatal cannabis exposure – The "first hit" to the endocannabinoid system. Neurotoxicology and Teratology. 2016;58:5-14.

https://doi.org/10.1016/j.ntt.2016.08.003

PMid:27567698

41. Fried PA, Makin JE. Neonatal behavioral correlates of prenatal exposure to marijuana, cigarettes and alcohol in a low-risk population. Neurotoxicology and Teratology. 1987;9:1-7.

https://doi.org/10.1016/0892-0362(87)90062-6

42. Coles CD, Platzman KA, Smith I, et al. Effects of cocaine and alcohol use in pregnancy on neonatal growth and neurobehavioral status. Neurotoxicology and Teratology. 1992;14:23-33.

https://doi.org/10.1016/0892-0362(92)90025-6

43. Dotters-Katz S, Smid M, Manuck T, et al. Risk of neonatal and childhood morbidity among preterm infants exposed to marijuana. J Matern Fetal Neonatal Med. 2017;30(24): 2933–2939.

https://doi.org/10.1080/14767058.2016.1269165

PMid:27921445 PMCid:PMC5612850

44. El Marroun H, Hudziak JJ, Tiemeier H, et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. Drug Alcohol Depend. 2011;118(2-3):470–474.

https://doi.org/10.1016/j.drugalcdep.2011.03.004

PMid:21470799

45. Goldschmidt L, Richardson GA, Willford J, et al. Prenatal marijuana exposure and intelligence test performance at age 6. J Am Acad Child Adolesc Psychiatry. 2008;47(3): 254–263.

https://doi.org/10.1097/CHI.0b013e318160b3f0

PMid:18216735

46. Fried PA. Ottawa Prenatal Prospective Study (OPPS): Methodological Issues and Findings – It's Easy to Throw the Baby out with the Bathwater. Life Sciences. 1995;56:2159-2168.

https://doi.org/10.1016/0024-3205(95)00203-I

47. El Marroun H, Brown Q, Lund I, et al. An epidemiological, developmental and clinical overview of cannabis use during pregnancy. Preventive Medicine. 2018;116:1-5.

https://doi.org/10.1016/j.ypmed.2018.08.036

PMid:30171964

48. Mehmedic Z, Chandra S, Slade D, et al. Potency trends of Δ9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. Journal of Forensic Sciences. 2010;55(5):1209-17.

https://doi.org/10.1111/j.1556-4029.2010.01441.x

PMid:20487147

49. American College of Obstetricians and Gynecologists. Committee Opinion – Marijuana Use During Pregnancy and Lactation. Washington DC. 2017 [accessed January 17, 2017]. Available from:http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Marijuana-Use-During-Pregnancy-and-Lactation.

The British Student Doctor, 2019;3(2):34-39
doi: 10.18573/bsdj.80
Education

Extending the frontiers of neuroimaging: an introduction to Diffusion Tensor Imaging Tractography

EDUCATION

AUTHOR

Anastasia Mirza-Davies
Cardiff University School of Medicine, UK

Dr Judith Harrison
Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, UK

Address for Correspondence:

Anastasia Mirza-Davies
Cardiff University, School of Medicine, Cochrane Building, Heath Park, Cardiff, CF14 4YU
Email: Mirza-DaviesA@cardiff.ac.uk

No conflicts of interest to declare

Accepted for publication: 31.01.19

ABSTRACT

Summary:

The use of Diffusion Tensor Imaging (DTI) tractography has exploded over the past two decades, proving to be a major advancement in the current methods for exploring the architecture of white matter tracts in the living human brain. Despite making up 50% of brain tissue, investigations into the function of white matter have long remained in the background of medical research. Consequently, white matter pathology cited in neuropsychiatric disease remains a heavy burden of human illness. Nonetheless, with novel diffusion MRI techniques, including DTI tractography, we are able to visualise areas of the brain better than ever before, furthering our understanding of white matter beyond the crude depictions offered by conventional MRI.

Relevance:

It is important that medical students have an understanding of DTI tractography because it has the potential to illuminate mechanisms that underpin cognition and emotion through the creation of connectional maps. Furthermore, advances in MR technology should not be restricted to the territory of academics. Instead, both medical students and clinicians should be able to draw upon the current research methods to improve the care and understanding of patients with white matter pathology.

Take-Home Messages:

1. Diffusion Tensor Imaging is a diffusion MRI technique that depicts the movement of water molecules along major white matter pathways in the living brain
2. Using information from DTI, tractography software virtually reconstructs white matter tracts and can be used to make dissections of major fasciculi in vivo.
3. DTI tractography remains the only non-invasive method to study white matter tracts in the living human brain
4. Results from tractography are increasingly being used in neuropsychiatric research
5. Despite its potential, DTI tractography still faces a number of challenges. The most prominent of these being its inability to accurately map crossing fibres within a voxel.

Neuroanatomists have worked to delineate the architecture of the human brain from as early as the 19th century. (1) Such techniques have ranged from classical studies of histological sections and post-mortem dissections, to the use of peroxide tracers that can be actively transported along axons. (2,3) Nonetheless, Diffusion Tensor Imaging (DTI) tractography, (4-7) a novel neuroimaging technique developed in the early 1990s, remains the only non-invasive method for exploring white matter connections in the living human brain. (8, 9)

Advances in Neuroimaging

Owing to recent advances in technology, clinicians now have access to an array of neuroimaging techniques that can explore brain structure. One of the earliest examples of this is computed tomography (CT). CT uses X-rays to visualise gross structures in the head such as bone and soft tissue. Whilst indispensable in emergency settings, CT is increasingly being replaced by magnetic resonance imaging (MRI). Unlike other scanning techniques, MRI is able to create contrast between soft tissue, allowing the naked eye to distinguish between white and grey matter. DTI is an MRI-based neuroimaging technique developed specifically to visualise myelinated tracts and macroscopic connectivity of the brain.

How does DTI work?

In order to understand DTI, its first important to know the basics of diffusion and how it varies across biological tissue.

In simple liquids and some homogenous solid materials water molecules are free to move equally in all directions. This is known as isotropic diffusion and is represented in figure 1.

However, due to the structure of axons, diffusion in the white matter of the brain is anisotropic, meaning the direction of diffusion is unequal. As the myelin surrounding axons is relatively impermeable to water, we can assume it acts as a barrier to diffusion. Therefore, whilst water is able to diffuse at high rates along the long axis of axons through the cytoplasm, diffusion perpendicular to the long axis is restricted. This is demonstrated in figure 1.

Diffusion Tensor Imaging works by tracing the motion of water molecules along axons; therefore the scanner is able to pick up diffusion in one direction. This is called setting a diffusion gradient. (10)

In 1994, Basser et al. (11) demonstrated that by utilising multiple diffusion gradients, DTI can be used to compute the principal 3D trajectory of white matter fibres in each MR voxel - known as a diffusion tensor. The diffusion tensor made it possible to display the orientation of major fasciculi in vivo (1) and a number of methods have since been developed to achieve this. (12-16) Colour coded 2D images produced in conjunction with priori knowledge of white matter anatomy have been favoured to detail the orientations of major white matter tracts (see figure 1.1).

Tractography Methods

Whilst novel, the poor visualisation of tracts in DTI led to the development of fiber tractography. Using tractography software, such as ExploreDTI (17), alongside the information obtained in Diffusion MRI, it is possible to employ algorithms that virtually reconstruct the 3D trajectories of neuronal fibre pathways in vivo. (18) These trajectories are often referred to as '*streamlines*.' (See figure 1.2)

There are currently two major classes of algorithms used in tractography. The first class, known as deterministic algorithms, (7,19,20) work on the assumption that the principal direction or eigenvector (PEV) of the diffusion tensor is parallel to the direction of most fibres running within a voxel. In this method, a number of seed points (starting voxels) are placed within the brain and the PEV is measured. Deterministic algorithms are then used to calculate how closely the orientations of neighboring voxels match the seed. Voxels with similar PEVs to the seed are subsequently connected bidirectionally to form streamlines.

Whilst deterministic algorithms have been shown to produce major reconstructions faithful to classic neuroanatomy; (1, 21, 22) this mode of tracking remains susceptible to false positives and often fails to account for branching fasciculi.

To overcome these limitations, a second class of probabilistic algorithms have since been developed for use in tractography. (23-26) Instead of relying upon the PEV, probabilistic tracking applies an orientation density function (ODF). This calculates the probability of multiple fibre pathways projecting from the seed points and again at each step along reconstructed streamlines. Not only does a probabilistic approach account for branching fasciculi but it is also able to quantify the confidence of each reconstructed pathway. (8) An example of streamlines produced by probabilistic tracking is shown in figure 1.2.

Potential clinical applications of DTI tractography

DTI has generated enormous research interest due to its ability to evaluate pathological changes in brain tissue. For example, diffusion MRI has been identified as a promising biomarker in neurodegenerative conditions such as Alzheimer's disease (AD). AD is defined by widespread cognitive impairments including

executive function failure, emotional instability and psychosis. (27) A longitudinal study (28) comparing imaging data of AD patients with controls showed that anisotropic diffusion was significantly reduced in those with AD. This was also associated with disease progression. Therefore, DTI not only has the potential to aid pre-symptomatic detection of AD, but it may also help to differentiate between mild cognitive impairment and early signs of AD. (29)

Another example of its potential use is in patients with Multiple Sclerosis (MS). Similar to AD, MS lesions are associated with reduced anisotropic diffusion. Some studies have therefore suggested that DTI can be used as a biomarker of disease activity in MS and will further enable clinicians to monitor disease progression. (27)

The challenges facing DTI tractography: Mapping the Superior Longitudinal Fasciculus

Despite its potential, DTI tractography still has a number of significant limitations. These become apparent when reconstructing complex association fibre bundles such as the superior longitudinal fasciculus (SLF). Thought to be involved in important cognitive processes such as attention, memory and language; the SLF has posed a particular challenge to researchers using tractography and this is reflected in the medical literature. For example, studies describing its cortical connections are often confusing or contradictory. (9, 30-32) As DTI has conventionally used a single tensor of diffusion per voxel, it is therefore unable to account for multiple fibres crossing or diverging within a voxel. (33) This becomes a major problem when mapping the SLF.

We know from classical post mortem studies that the SLF intersects the fronto-occipital fasciculus at the level of the frontal operculum. (34) As a result, dissections are often inaccurate as crossing fibres artificially deviate reconstructed trajectories towards closer endpoints. (35) Furthermore, DTI-tractography is not yet sensitive enough to distinguish between separate fascicles in areas where tracts run parallel, resulting in numerous false positives. Running closely alongside both the optic radiations and the inferior fronto-occipital fasciculus, (1,34) the SLF again offers an important example of this.

Ultimately the inability of tractography to map complex white matter pathways, such as the SLF, call into question whether tractograms reflect true neuroanatomy, let alone their use as a tool for quantitative analysis.

Conclusion: The future of DTI tractography

Albeit, more research is needed to overcome the shortcomings of tractography, it is undeniable that Diffusion MRI has the potential to revolutionise the way in which we study white matter. In particular, a number of studies have highlighted its promise as a biomarker in neurodegenerative disease. Ultimately, this can help pave the way for new, much needed treatments and improved patient care.

Figures

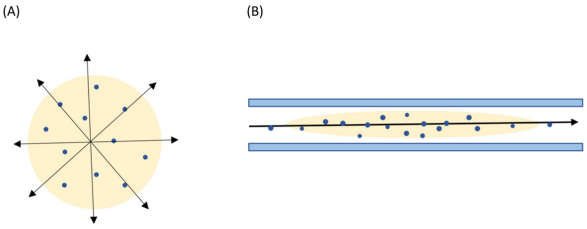

Figure 1: (A) Showing isotropic diffusion. As there are no barriers, water molecules are free to diffuse in all directions. Diffusion in the CSF and grey matter is primarily isotropic. (B) Showing anisotropic diffusion. The myelin sheath surrounding axons acts as a biological barrier to diffusion. Diagram based on Wilde et al. 2017.

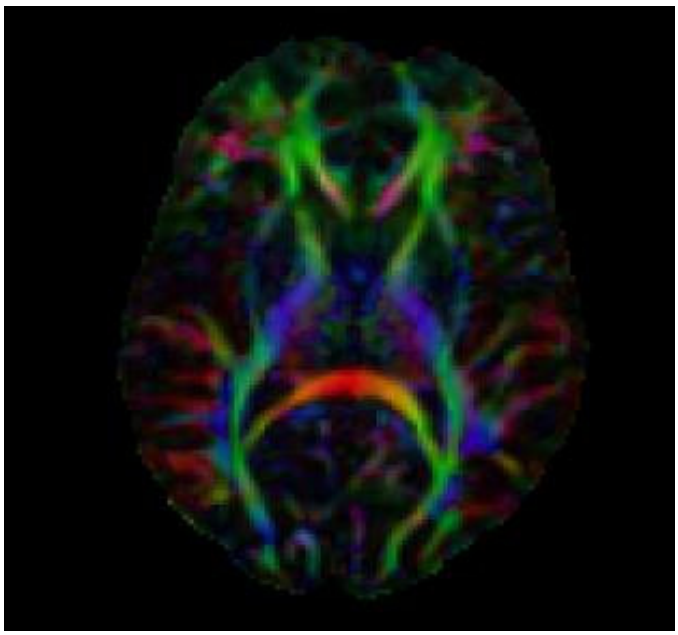

Figure 1.1: showing a Diffusion Tensor. It is colour coded to show the principal direction of white matter tracts. Red represents left to right, blue shows cranial to caudal and green depicts tracts running anterior to posterior. Data courtesy of the University Medical Centre Utrecht Explore DTI Workshop.

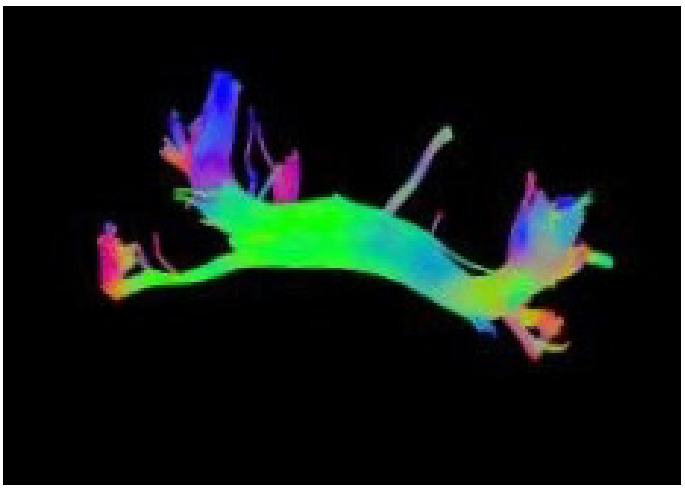

Figure 1.2: showing a reconstruction of the SLF 1 using probabilistic tractography. Data courtesy of the University Medical Centre Utrecht Explore DTI Workshop.

References

1. Catani M, Howard R, Pajevic S, Jones D. Virtual in Vivo interactive dissection of the white matter fasciculi in the human brain. Neuroimage. 2002;17:77-94.

https://doi.org/10.1006/nimg.2002.1136

PMid:12482069

2. Cohen W, Cuénod M. The use of Axonal Transport for Studies of Neuronal Connectivity. Amsterdam: Elsevier;1975.

3. Heimer J, Robards M. Neuroanatomical Tract-Tracing Methods. New York: Plenum;1981.

4. Basser P. Fiber-Tractography via diffusion tensor MRI (DT-MRI). In Book of Abstracts: Sixth Annual Meeting of the International Society for Magnetic Resonance in Medicine. Berkley, CA: ISMRM 1998.

5. Jones D, Simmons A, Williams S, Horsfield M. Non-invasive assessment of structural connectivity in white matter by diffusion tensor MRI. In Book of Abstracts: Sixth Annual Meeting of the International Society for Magnetic Resonance in Medicine. Berkley, CA: ISMRM 1998.

https://doi.org/10.1002/(SICI)1522-2594(199907)42:1<37::AID-MRM7>3.0.CO;2-O

6. Jones D, Simmons A, Williams S, Horsfield M.Non invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magnetic Resonance Medicine. 1999;42:37-41.

7. Basser P, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magnetic Resonance Medicine. 2000;45:788-796.

https://doi.org/10.1002/1522-2594(200010)44:4<625::AID-MRM17>3.0.CO;2-O

8. Jones D. Tractography gone wild: probabilistic fibre tracking using the wild bootstrap with diffusion tensor MRI. IEEE Transactions on Medical Imaging .2008;27:1268-1274.

https://doi.org/10.1109/TMI.2008.922191

PMid:18779066

9. Catani M, Thiebaut De Schotten M. A diffusion tensor imaging atlas for virtual in vivo dissections. Cortex. 2008;44:1105-1132.

https://doi.org/10.1016/j.cortex.2008.05.004

PMid:18619589

10. Moseley M, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari H, Wendland M, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology. 1990;176:439-445.

https://doi.org/10.1148/radiology.176.2.2367658

PMid:2367658

11. Basser P, Matiello J, Le Bihan D. Estimation of the effective diffusion tensor for the NMR spin echo. Journal of Magnetic Resonance. 1994;103:247-254.

https://doi.org/10.1006/jmrb.1994.1037

PMid:8019776

12. Basser P, Pierpaolli C. Elucidating tissue structure by diffusion tensor MRI. In Book of Abstracts: Third Annual Meeting of the International Society for Magnetic Resonance in Medicine. Berkley, CA: ISMRM:1995.

13. Nakada H, Matsuwaza H. Three dimensional anisotropy contrast magnetic resonance imaging of the rat nervous system: MR axonography. Neuroscience Resonance. 1995;22:389-398.

https://doi.org/10.1016/0168-0102(95)00917-I

14. Jones D, Williams S, Horsfield M. Full representation of white matter fibre direction on one map via diffusion tensor analysis. In Book of Abstracts: Fifth Annual Meeting of the International Society for Magnetic Resonance in Medicine. 1997.Berkley, CA: ISMRM

15. Pajevic S, Pierpaoli C. Colour schemes to represent the

orientation of anisotropic tissues from diffusion tensor data: Application to white matter fibre tract mapping in the human brain. Magnetic Resonance Medicine. 1999;42:526-540.

https://doi.org/10.1002/(SICI)1522-2594(199909)42:3<526::AID-MRM15>3.0.CO;2-J

16. Pajevic S, Pierpaoli C. Colour schemes to represent the orientation of anisotropic tissues from diffusion tensor data: Application to white matter fibre tract mapping in the human brain. Magnetic Resonance in Medicine. 2000;43:921.

https://doi.org/10.1002/1522-2594(200006)43:6<921::AID-MRM23>3.0.CO;2-I

17. Leemans A, Jeurissen B, Sijbers J, Jones DK. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: 17th Annual Meeting of Intl Soc Mag Reson Med; 2009 p. 3537.

18. Leemans A. Visualization of Diffusion MRI Data. The Functional Anatomy of White Matter: From Postmortem Dissections to In Vivo Virtual Tractography. In: Jones D. Diffusion MRI. Oxford: Oxford University Press;2010.

19. Mori S, Crain B, Chacko V, van Zijl P. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Annals Neurology. 1999;5:265-269.

https://doi.org/10.1002/1531-8249(199902)45:2<265::AID-ANA21>3.0.CO;2-3

20. Lazar M, Weinstein D, Tsuruda J, Hasan K, Arfanakis K, Meyerand E, Badie B, Rowley H, Haughton V, Field A, Witwer B, Alexander A. White matter tractography using tensor deflection. Human Brain Mapping. 2003;18:306-321.

https://doi.org/10.1002/hbm.10102

PMid:12632468

21. Mori S, Kaufmann W, Davatzikos C, Stieltjes B, Amodei L, Fredericksen K, Pearlson G, Solaiiyappan M, Raymond G, Moser H, and van Zijl P. Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. Magnetic Resonance Medicine. 2002;47:215-223.

https://doi.org/10.1002/mrm.10074

PMid:11810663

22. Lawes I, Barrick T, Murugam V, Spierings N, Evans D, Song M. Atlas-based segmentation of white matter tracts of the human brain suing diffusion tensor tractography and comparison with classical dissection. Neuroimage. 2008;39:62-79.

https://doi.org/10.1016/j.neuroimage.2007.06.041

PMid:17919935

23. Firman O, Farneback G, Westin C. A Bayesian approach for stochastic white matter tractography. IEEE Transactions on Medical Imaging. 2006;25:965-978.

https://doi.org/10.1109/TMI.2006.877093

24. Hagmann P, Thiran JP, Jonasson L, Vandergheynst P, Clarke S, Maeder P, et al. DTI mapping of human brain connectivity: statistical fibre tracking and virtual dissection. NeuroImage. 2003;19:545-554.

https://doi.org/10.1016/S1053-8119(03)00142-3

25. Jones D, Knösche T, Turner R. White matter integrity, fibre count and other fallacies: the do's and don't's of diffusion MRI. Neuroimage. 2013;73:239-254.

https://doi.org/10.1016/j.neuroimage.2012.06.081

PMid:22846632

26. Lazar M, Alexander A. Bootstrap white matter tractography (BOOT-TRAC).NeuroImage. 2005;24:524-532.

https://doi.org/10.1016/j.neuroimage.2004.08.050

PMid:15627594

27. Woo-Suk T, Byung-Joo H, Sung-Bom P, Shin-Hyuk K, Byung-Jo K. Current Clinical Applications of Diffusion-Tensor Imaging in Neurological Disorders. Journal of Clinical Neurology. 2018;14:129-140.

https://doi.org/10.3988/jcn.2018.14.2.129

PMid:29504292 PMCid:PMC5897194

28. Mayo C, Mazerolle, E, Ritchie, L, Fisk, J, Gawryluk, J. Longitudinal changes in microstructural white matter metrics in Alzheimer's disease. Neuroimage: Clinical. 2017;13:330-338.

https://doi.org/10.1016/j.nicl.2016.12.012

PMid:28066707 PMCid:PMC5200876

29. Nowrangi MA, Rosenberg P. The fornix in mild cognitive impairment and Alzheimer's disease. Frontiers in Aging Neuroscience. 2015;7:1-7.

https://doi.org/10.3389/fnagi.2015.00001

PMid:25653617 PMCid:PMC4301006

30. Fernandez-Miranda J, Rhoton A, varez-Linera J, Kakizawa Y, Choi C, de Oliveira E.Three-dimensional microsurgical and tractographic anatomy of the white matter of the human brain. Neurosurgery. 2008;62:989-1026.

https://doi.org/10.1227/01.neu.0000333767.05328.49

PMid:18695585

31. Barrick T, Lawes I, Mackay C, Clark C. White matter pathway asymmetry underlies functional lateralization. Cerebral Cortex. 2007;17:591-598.

https://doi.org/10.1093/cercor/bhk004

PMid:16627859

32. Bernal B, Ardila A. The role of the arcuate fasciculus in conduction aphasia. Brain. 2009;132:2309-2316.

https://doi.org/10.1093/brain/awp206

PMid:19690094

33. Descoteaux M, Deriche R, Knosche T, Anwander A. Deterministic and probabilistic tractography based on complex fibre orientation distributions. IEEE Transactions on Medical Imaging. 2009;28:269–286.

https://doi.org/10.1109/TMI.2008.2004424

PMid:19188114

34. Martino J, Witt Hammer P, Berger M, Lawton M, Arnold C, Lucas E, et al. Analysis of the sub components and cortical terminations of the perisylvian superior longitudinal fasciculus: a fiber dissection and DTI tractography study. Brain Structure and Function. 2013;218:105-121.

https://doi.org/10.1007/s00429-012-0386-5

PMid:22422148

35. Bernal B, Altman N. The connectivity of the superior longitudinal fasciculus: a tractography DTI study. Magnetic Resonance Imaging. 2010;28:217-225.

https://doi.org/10.1016/j.mri.2009.07.008

PMid:19695825

The British Student Doctor, 2019;3(2):40-41
doi: 10.18573/bsdj.88
Reflections

The dead shall entertain the living: '*Bodyworlds*' from the perspective of medical students

REFLECTIONS

AUTHOR

Emma Norton
St George's University of London

Harry Davies
St George's University of London

Address for Correspondence:

Emma Norton
St George's University of London,
Cranmer Terrace, London, SW17 0RE

Email: m1401333@sgul.ac.uk

No conflicts of interest to declare

Accepted for publication: 25.02.19

On October 6th, Gunther von Hagens' extravagant exhibit of human dissections, *Bodyworlds*, opened in London's Piccadilly Circus. After drawing the attention of the nation in 2002 with the first public autopsy in 170 years, von Hagens now presents his tour of the human body hoping to "*edutain*" (educate and entertain). Since 1995, '*Bodyworlds*' has been renowned for the dramatic and often shocking poses of its plastinated cadavers. We entered Bodyworlds prepared to expand our anatomical knowledge but also mire at the craftsmanship of his preparations. In this article, we explore the educational value and ethical considerations surrounding an exhibition like *Bodyworlds* from the perspective of penultimate year medical students.

The exhibition was separated into organ systems with relevant pathological prosections dominating each display. This arrangement was genuinely educational at the level of the layperson and conveyed health promoting ideas. Typical of this was the interactive display showing the detriments of smoking. To the general public, witnessing a fully dissected nervous system or an infarcted heart offered a novel, engaging and genuinely educational experience. As medical students, we take these opportunities for granted but on first exposure, they will leave visitors with a lasting impression of the human form and its mortality. As important as this is, our own knowledge was not expanded beyond that of introductory sessions held in our first years at medical school. It may have been presumptive of us to expect a post-graduate level of anatomical and physiological content, nonetheless, we felt disappointed that plastination was not used to its full potential. To us, it could revolutionise anatomical teaching by displaying delicate anatomy in ways not possible through traditional methods. We left feeling this was a missed opportunity. Anatomical labels were haphazardly scattered on some specimens as if randomly drawn from von Hagens' signature hat.

The exhibition quickly turned to the more bizarre imaginings of von Hagens' brain, with dissections becoming less and less relevant, and more and more striking. It was difficult to see the educational value of "*Atlas*", a cadaver positioned carrying a replica of the Earth, complete with suspiciously attached Mohawk. The question of whether body donors knew of their eventual post-mortem positioning struck us throughout the exhibition. We were answered in a short video where von Hagens stated that the positioning of "*Atlas*" was devised post-dissection after remarking at his muscular physique. It should be noted that *Bodyworld* donors can consent to public display as an "*anatomical work of art*" but beyond this, it is unclear how much input they have. In honesty, we were surprised to learn that the Institution of Plastination has over 17,000 registered donors despite this. (1) For us, this strikes few parallels with the world of medicine where informed consent is emphasised to the highest degree. This contrast was highlighted around a poker table where three dissected bodies were placed as if re-enacting a James Bond scene. All educational value had been abandoned in place of spectacle when we saw a man riding an enormous horse whilst holding his own, and the horse's, brain aloft for our viewing pleasure.

Seeing a human body presented in this way evokes an emotional rollercoaster, from awe at the dramatic posing, to the realisation that these bodies were donated by once living people. Even as medical students with years of anatomical experience, we were not immune to this human reaction. We were impressed by the technical brilliance and spectacle of the dissections but also felt conflicted at how they were presented. For example, the decision to display a pregnant woman, with a viewing window cut into her abdomen revealing her unborn child, left us uneasy. Our emotional responses, perhaps, were heightened from our previous experiences of dissection. We always treat the dead with the utmost respect and dignity, with emphasis on respectful handling of human remains. Interestingly, when *Bodyworlds* underwent an ethical review by the California Science Center in 2004, the committee deemed there to be an atmosphere of respect. (2) To us, these sentiments seemed fleeting throughout *Bodyworlds*, which arguably embraced more sentiments of a showroom, rather than a dissecting room.

Some sections were less enjoyable to view and were more ethically problematic. Plastinated foetuses of just a few weeks gestation isolated in glass cases were presented with little educational comment. One of the key recommendations of the California Science Center's review was the presence of accompanying text panels of adequate information. The plastinated foetuses were not displayed in California. (2) It's hard to place why they were so upsetting, but the lack of educational effort in this section was much more hurtful. We were concerned that donor consent was only mentioned once within the exhibit – for two lovers immortalised in sexual intercourse - as if the other positionings and specimens did not warrant such ethical consideration. This lack of emphasis on consent again flies in the face of our medical teaching. The relative lack of transparency was uncomfortable as if they are trying to hide this aspect of the process from the public eye. We felt there was a missed opportunity to educate the public about the process and benefits of body donation. *Bodyworlds* is a unique spectacle in bringing attention to body donation but does little to promote it as a way to further medical education.

Bodyworlds was an experience not to be missed, best described by its creator as "*edutainment*". It sparked many ethical discussions between us, mostly centred on consent, respect and whether education prevails in justifying the exhibit. Nonetheless, *Bodyworlds* has undergone worldwide ethical scrutiny in the public and scientific eye. To our eyes, it seemed more concerned with the spectacle and showmanship than the informative text panels. It is tempting to ask whether this detracts from the great educational potential '*Bodyworlds*' has. Without this extravagance, however, it would be unlikely to engage half the audience it has since 1995. It is also poignant to remember that the history of anatomy is rooted in artistic expression and has been since the days of Galen and Vesalius. Many questions remain – art or science, education or entertainment and why where there swings halfway through the exhibit?

References

1. Body Worlds. Vital Donor Programme. London: Body Worlds; 2018 [accessed 10 Jan 2019]. Available from: https://www.bodyworldsvital.com/about-us/donors/.

2. California Science Center Ethics Committee. Body Worlds: An Anatomical Exhibition of Real Human Bodies Summary of Ethical Review. Los Angeles: California Science Center; 2004 [accessed 10 Jan 2019]. Available from: https://californiasciencecenter.org/file/summary-of-ethical-review-updatepdf.

Editorial Note: The 'Bodyworlds' press office was contacted in February 2019 for a response to this article, with the offer to publish their response in the journal. To date, no response has been received.

The British Student Doctor, 2019;3(2):42-45
doi: 10.18573/bsdj.77
Reflections

The kind assailant: how dementia patients view their carers

REFLECTIONS

AUTHOR

Dr Mustafa Omar Abdimalik
Betsi Cadwaladr University Health Board

Address for Correspondence:

Dr Mustafa Omar Abdimalik
Betsi Cadwaladr University Health Board
Ysbyty Gwynedd
Penrhosgarnedd, Bangor
Gwynedd
LL57 2PW

Email: abdimalik@doctors.org.uk

ORCID ID: 0000-0003-4043-7605

No conflicts of interest to declare

Accepted for publication: 02.09.18

A day on the wards

It is another day on the ward with many tasks to complete. I am a final year medical student who is working hard to be an effective member of the team on a care of the elderly ward. As I work attentively and swiftly to complete the morning jobs, a nurse interjects. She explains that she needs to give a patient an antibiotic, but their IV access is no longer functioning. However, realising that this patient needs their medication I decide to reprioritise. I proceed to the clinical room; assemble all required equipment for the insertion of a cannula and attend to the patient. The patient appears confused and although I try my best to obtain informed consent for the procedure, all I receive is a nod. An inquisitive one at best. Upon reflection, I know that I must proceed as it is in the patient's best interest.

As I start to insert the needle the patient grimaces and clearly looks uncomfortable. I apologise as I failed to insert the cannula. I decide to try again, and I receive the same puzzled look when asking for consent. I proceed once more and unfortunately; it is unsuccessful again. The patient appears uncomfortable and agitated. I apologise and stop. This bewildered patient is subjected to pain and while it seems justifiable, there is little I could do to reassure the patient.

Unfortunately, this was only the start of my patient's problems. The following week their fluid intake diminished, and the blood tests confirmed dehydration. At the same time one of the patients in the bay developed influenza. As such, the bay was "*isolated*". All staff members were required to wear an apron, face mask and gloves to enter the bay. This is required to prevent spread of a potentially lethal infection. If this wasn't enough, three patients then refused medications, two others refused blood tests and one patient declined cannulation - despite being counselled that it was required for an imminent CT scan. It felt like the

whole bay was rebelling.

Understandably, any confused individual, unsure of their surroundings and potentially unaware of what is taking place would feel distressed and overwhelmed, if they are suddenly approached with masked individuals with needles.

What barriers exist in communication with patients who have cognitive impairment?

These two encounters encouraged me to think about the difficulties in communicating with patients that have cognitive impairment. During early stages of disease patients with dementia suffer from anomia, literal and neologistic errors, and impairment in comprehension. The level of deterioration in the comprehension and expression of language is closely associated to the global severity of dementia. Rousseaux et al. have also shown that such patients tend to end conversations in requests rather than assertions, which can have implications in obtaining consent as well as understanding patient's preferences. (1) Additionally, the impairment affects both the receiving and relaying aspects of communication.

Research carried out by Machiels et al. (2017) has shown that there is a paucity of healthcare professionals with good skillset in communicating with cognitively impaired patients. (2) Complicating factors like heavy workload are present and this limits availability to attend to their patients. For instance, nurses have consistently raised concerns over large volumes of paperwork that have this effect. Additionally, difficulties experienced in communicating with patients have often led to observed reduction in patient-carer interactions and care. This is largely attributed to elevated levels of stress that healthcare professionals experience while managing patients with cognitive impairment. (3) Patients with Lewy body dementia often struggle with fluctuating cognition that primarily affects executive function and attention. Thus, patients lack the ability to follow commands or understand what others try to tell them, which increases frustration for the patients and healthcare professionals. (4)

Symptoms of dementia are influenced by the interplay of biological, social and psychological factors. These patients are less able to cope with the stresses that can arise from day to day changes in care and interactions with new members of the healthcare team. In addition, when such stress is recognized, it is often ignored or managed by reassuring the patient. However, this only serves to distract the patients from the stressful experiences rather than addressing them. (5) In my experience, this was seen in the instances when patient ask about if their spouses were visiting soon. The usual reply from caring staff being "*I am sure they will show up*", even if no visit was planned for that day.

Additionally, patients with dementia are more likely to show neuropsychiatric and behavioural symptoms during a period of transition; such as a hospital admission. This is particularly troublesome as the patients often have little preparation for this. Swift changes of environment are often psychologically demanding for the patients with cognitive impairment. (6)

Cognitive impairment often leads to anxiety, apathy, irritability and sorrow, which increase the risk of depression and exacerbate behavioural changes. The risk of these changes significantly increase as the severity of the underlying condition worsens. According to Wragg et al. up to 50% of all patients with Alzheimer's disease suffer from depression while the frequency of delirium with visual and auditory hallucinations vary between 10-73%. (7) During these periods of high level of impairment, communication is very difficult and drug therapy is often prescribed. However, often they have little role in treating the patient and rather, it is for the benefit of other patients and staff. (8)

It is generally accepted that healthcare professionals tend to have less confidence in recognising symptoms of depression, or even pain, while treating patients with cognitive impairment. This is attributed to patient's limited ability to vocalise such symptoms. As a result, there is growing concern that the methods of communication used are inadequate in addressing concerns of patients with cognitive impairment. Therefore, greater knowledge and experience is required to ensure that the level of communication is appropriate, and this level is dependent on the condition of the patient. (9)

What can healthcare professionals do to improve communication with patients who have cognitive impairment?

NICE guidelines encourage delivering patient-centred care in which the human value of the patient, their individuality and relationship with others are respected. (10) This communication is effective due to these following reasons:

- By respecting the human value of the patient, the severity of their cognitive impairment does not lead to less care or negligence. In fact, it promotes care delivery in which communication is appropriate and considerate of the level of impairment.
- Allowing patients to communicate their understanding of the disease while appreciating that their personality and pervious experiences helped shape that understanding.

• Healthcare professionals should work as part of a team that include family and carers to build relationships that promote patient's well-being. (10)

Healthcare professionals should avoid modifying their speech and language using assumptions based on the outer appearance of patients and age. Communication is often stereotyped when healthcare professionals interact with older patients, as a result of presumed or imagined deficits. Subsequently, patients face staff who use high pitch sound, diminutive naming, simple vocabulary, exaggerated intonations and exaggerated praise. All of these can lead to reduced sense of personal control and withdrawal from activities. Equally, over-accommodating of patients' needs might lead to a negative effect on communication. For example, Savundranayagam et al. showed that elaboration and repetition was helpful in aiding understanding, but short sentences can often be interpreted as directive and conveying negative messages. (11)

Patients with cognitive impairment require adaptable communication that takes into account their personal history and communication strengths. It should promote the individuality that makes care more relevant and communication more successful. Stereotyped forms of communication may be perceived as patronising and often lead to a breakdown of trust and resistance to care. (12)

Communication is not a simple process and a successful clinician is able to adapt to different situations and is alert to the varying needs of different patients. However, it can be difficult on occasions to ascertain what the patient might specifically require. During such cases, family members and carers can provide an insight to the patients need. As such, it is important that good relationships are built and maintained with carers and family members to ensure optimal care is provided. (13)

Effective communication is a crucial aspect of care as it allows clinicians to facilitate appropriate treatments. Equally, it helps patients understand their therapy and improve concordance. Many patients can have similar presentations and diagnoses, but patients' experiences of these are rarely identical. Subsequently, we should all listen and be able to adapt to communication needs. By appreciating the personal aspects of patients' care, we can optimise our communication – this is especially vital when caring for patients with cognitive impairment.

My experience as a student have helped me appreciate communication challenges that can present while caring for patients. Understanding disease process and their effect on patients is crucial, however, good communication skills are essential and the key factor in delivering personalised care.

References

1. Rousseaux M, Seve A, Vallet M, Pasquier F, Mackowiak-Cordoliani M. An analysis of communication in conversation in patients with dementia. Neuropsychologia. 2010; 48(13):3884-90.

https://doi.org/10.1016/j.neuropsychologia.2010.09.026

PMid:20888846

2. Machiels M, Metzelthin SF, Hamers JPH, Zwakhalen SMG. Intervention to improve communication between people with dementia and nursing staff during daily nursing care: A systemic review. International Journal of Nursing Studies. 2017;66:37-46.

3.Keenan GM, Yakel E, Tschannn D, Mandeville M. Documentation and the Nurse Care Planning Process. In: Hughes RG, editor. Patient Safety and Quality: and Evidence- Based Handbook for Nurses. Rockville: Agency for Healthcare and Quality; 2008.

4. Kobeleva X, Firbank M, Peraza L, Gallaghar P, Thomas A, Burn DJ, O'Brien J, Taylor J. Divergent functional connectivity during attentional processing in Lewy body dementia and Alzheimer's disease. Cortex. 2017;92:8-18.

https://doi.org/10.1016/j.cortex.2017.02.016

PMid:28391039 PMCid:PMC5480774

5. Melo G, Maroco J, Lima-Basto M, de Mendonca A. Personality of the caregiver influences the use of strategies to deal with behaviour of persons with dementia. Geriatric Nursing. 2017;38:63-69.

https://doi.org/10.1016/j.gerinurse.2016.08.001

PMid:27590309

6. Muller C, Lautenschlager S, Meyer G, Stephan A. Intervention to support people with dementia and caregivers during the transition from home to nursing home care: a systemic review. International Journal of Nursing Studies. 2017;71:139-152.

https://doi.org/10.1016/j.ijnurstu.2017.03.013

PMid:28411508

7. Wragg RE, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. Am J Psychiatry. 1989;146(5);577-87.

8. Evans J. The Ethics of Antipsychotics in Alzheimer's disease. Caring for the Ages. 2011;12(5):27.

9. Brody A, Guam C, Cortes Tara, Galvin J. Development and testing of the Dementia symptom management at home (DSM-H) program: An interprofessional home healthcare intervention to

improve the quality of life for persons with dementia and their caregivers. Geriatric Nursing. 2016;37:200-206.

https://doi.org/10.1016/j.gerinurse.2016.01.002

PMid:26922312

10. National Institute for Health and Care Excellence. Dementia: Supporting people with Dementia and their carers in health and social care. London: NICE; 2006 [accessed 28 Apr 2017]. Available from: https://www.nice.org.uk/guidance/cg42.

11. Savundranayagam MY, Ryan EB, Anas AP, Orange JB. Communication and Dementia: Staff Perceptions of Conversational Strategies. Clinical Gerontologist. 2008;31:47-63.

https://doi.org/10.1300/J018v31n02_04

12. Williams KN, Herman R, Gajweski B, Wilson K. Elder speak communication: Impact on dementia care. American Journal of Alzheimer's Disease & Other Dementias. 2009;24(1):11-20.

13. Schmidt KL, Linger JH, Schulz R. Verbal communication among Alzheimer's disease patients, their care givers, and primary care physicians during primary care office visits. Patient Education and Counselling. 2009;77:197-201.

https://doi.org/10.1016/j.pec.2009.03.023

PMid:19395224 PMCid:PMC2839539

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