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Editorial

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Welcome to the January 2021 issue of The British Student Doctor Journal!

In our editorial a year ago, we looked ahead to a new decade full of challenges; however, 2020 managed to trump all but the wildest predictions. We would like to extend our heartfelt thoughts and wishes to all those who have been tragically affected by this pandemic, lost loved ones, their good health, financial stability and so many other things. Furthermore, sincere thanks are owed to the many healthcare professionals and other key workers who have worked so hard throughout this pandemic to protect, care and serve society.

This issue features a guest editorial by Dr Ed Cantelo, co-founder of Medics' Money, who writes about a topic that often goes under the radar in medical training: doctors' finances. His piece takes a very useful and practical approach, which readers at all stages of training will certainly find informative.

In the Original Research section of this issue, Hannah Withers and colleagues from the University of Birmingham, share a review of the evidence on the best treatment of post-stroke depression. Depression is a common facet of the aftermath of a stroke, and its treatment is often overlooked, possibly resulting in worse outcomes in terms of rehabilitation and recovery. Critically reviewing guidelines is a very important skill for any physician, and Withers and colleagues have demonstrated an excellent example of this with their insightful study.

Further, we feature a high-quality study by Lianne Fakes and colleagues from Cardiff University, entitled "The role of the glucocorticoid receptor in anti-hormone resistance in breast cancer". Breast cancer being another commonly encountered condition, this is an important piece elucidating a key mechanism of resistance to common oncological treatments.

While reviewing the management of common conditions and finding new ways of enhancing diagnosis and treatment constitutes a critical part of medical research and practice, rare conditions can be difficult to diagnose and it can often take years or even decades for sufferers to receive a diagnosis. Improving teaching of rare disease may make a substantial difference to these sufferers, as Lucia Lazzereschi from the University of Southampton writes in her Discussion Starters piece.

In the title piece of this issue, Ryan McFall updates our readers on the hot topic of antimicrobial resistance and summarises current approaches on tackling this critical issue. Through this, McFall tackles the key theories that underpin modern antimicrobial stewardship; an issue that is more important today than ever before with the ever-increasing rise in multi-drug resistant organisms seen in clinical practice.

Our Education section additionally features a piece on scabies, focussing on its epidemiology, pathogenesis and treatment. Adnan Haseeb Hussain and colleagues provide important insights into a common but often overlooked condition in medical education, providing the key information to appropriately equip students and doctors if they encounter it in their practice.

Another outstanding addition to this year's January issue is Callum Phillips' guide on informed consent. This is an important piece on a pertinent topic, and relevant not just to medical students but for the whole of the healthcare professional community, regardless of specialty or stage of training.

Finally, we feature an article that is perhaps especially important in the current times, which is Haroon Ali Shah, Yasmin Gabrielle Nikookam and Riaz Nawaz's Reflection piece, making a case for instating a wellbeing representative at medical schools. With COVID-19 affecting medical education and the mental health of medical students in an unprecedented manner, this interesting proposal is certainly well worth a read.

We hope you enjoy this January issue of The British Student Doctor Journal. We would like to thank each and every member of our superb editorial team for their hard work and dedication, as well as our peer reviewers, faculty advisor board and publisher, Cardiff University Press. Finally, thank you also to you, our faithful readers!

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Editorial

Why money matters? What medical school doesn't teach you

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As part of my Foundation Programme induction in A&E we were asked the question that still strikes dread into my heart: 'give one interesting fact about yourself'. I racked my brain for an 'interesting' answer. Eventually, I settled on telling the group "I used to be a chartered accountant and chartered tax advisor for nine years." Word of this soon got around and Tommy also knew by the time we met.

Dr Tommy Perkins was a locum doctor at the St Richard's Hospital in Chichester, where I had started my second year of the Foundation Programme. Before I arrived, he was helping his friends claim back tax on their professional expenses. We both shared a common goal that we wanted to help doctors make better financial decisions, which led us to co-found Medics' Money, a company with the objective of informing and empowering doctors to improve their 'financial health'.

As medical students we receive a lot of medical training, that is the point of medical school. One thing we do not get, however, is any "financial education" and this continues as you become a Foundation Doctor and move into the next stages of your training. This can mean that doctors often overpay income tax and National Insurance contributions when they start employment. They can end up confused regarding their pay and obligations, for example: 'do you need to tell HM Revenue and Customs if you receive a cheque for completing a cremation form?', or 'how does the pension scheme work?' - you may have seen the problems this has been causing for our senior colleagues in the press.

There are other good reasons to be more financially aware. We live in challenging times for a number of reasons, but doctors are fortunate in that their jobs should be safe whatever the future throws at us. However, over the last 10 years, the pay of some doctors has dropped 30% in real terms, according to the BMA. (1) If you live in an area with a high cost of living, like London or the South East, it's likely that the problem is even worse. If you add in the rising cost of medical school, junior doctor training and the increasing pension contributions with punitive taxation it's clear now, more than ever, that doctors of all ages need to be financially astute and there is no better place to start thinking about this than at medical school. Indeed, the cost of training is rising and the recent Health Education England document on 'Enhancing Junior Doctors' Working Lives' identified 'rising costs of developing as a professional' as a significant cause of low morale. (2) Surprisingly this document did not mention that claiming tax back on professional expenses could make training up to 40% cheaper. Unfortunately, a lot of the information provided to doctors to help them claim is out of date and unnecessarily onerous. Most of this information is vague, incomplete or simply incorrect.

So, what do you need to know now?

Of course, your focus will be on your medical studies but here are some important things to think about:

1) Once you start working as a doctor, you will be able to claim a tax deduction against your earnings for income tax purposes for any professional expenses you incur. Keep every receipt for every professional expense that you suffer. When you pay money to the GMC, the MDU or MPS, the BMA (if you choose to join) and later on the Royal Colleges, you can claim tax back on these expenses further down the line. This may seem like common sense but it's easy to forget to do this and then struggle to remember how much you paid. Unfortunately, you cannot get any money back for expenses you incur as a student.

2) Similarly, it is really important to keep a copy of all the payslips you receive. You may receive this electronically or in paper form. You will also receive various tax documents through your working career including P60s (a document you get at the end of each tax year to summarise everything regarding your income, tax, pension contributions and student loan contributions for the tax year) and P45s (a document you receive every time you change between employers). If in doubt keep it – you'll potentially need this information down the line, e.g. when applying for a mortgage.

3) As doctors, it is not uncommon for us to change jobs often. When we move employers (change Trusts), this can then have tax implications. This is mainly because of the confusion it causes in HM Revenue and Customs. I won't go into the details here but the main thing you need to know is that you should keep a close eye on the last payslip you receive from the old Trust and the first payslip of the new Trust – if you notice a marked difference in your tax bill or net pay you have the wrong "tax code" and need to get it changed.

4) It's always a good idea to continue the frugal habits you will acquired as a student into your employment years. For a variety of tips regarding keeping your finances healthy, we would recommend you download the following e-book: https://www.medicsmoney.co.uk/ebook/

When you're ready to know more, our company, set up by doctors for doctors, has a website (www.medicsmoney.co.uk) with a lot of free information on UK taxation, the NHS pension scheme and financial advice (including the "tax code" problem mentioned above). And, if you ever need more help than that, we have found some specialist medical accountants and Independent Financial Advisors that can help you with anything from tax returns to getting Income Protection.

With doctors' wages falling by up to 30% in 10 years, according to the BMA, combined with the rising cost of training for junior doctors, the loss of free accommodation, the pensions charges affecting our senior colleagues, among other things, it is important to do everything possible to mitigate the impact of declining incomes and rising tax bills. We cannot immediately change how doctors are remunerated, so a good financial plan is key to making the most of their earnings. Doctors often shy away from having conversations about finance, it's almost hardwired in us – but it's about time we understand our own ideas, concerns and expectations about our income and financial health.

REFERENCES

1. British Medical Association. Doctor's annual pay review from DDRB. London: British Medical Association; 2020 [accessed 11 Jan 2021]. Available from: https://www.bma.org.uk/pay-and-contracts/pay/how-doctors-pay-is-decided/doctors-annual-pay-review-from-ddrb.

2. Health Education England. Enhancing Junior Doctors' Working Lives. Leeds: Health Education England; 2020 [accessed 11 Jan 2021]. Available from: https://www.hee.nhs.uk/our-work/doctors-training/enhancing-working-lives.

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Original Research

The effectiveness of cognitive behavioural therapy versus antidepressants for treatment of post-stroke depression in adults

ORIGINAL RESEARCH

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ABSTRACT

Stroke is a common disorder with profound lasting effects and the UK's fourth leading cause of morbidity. One important after-effect is post-stroke depression (PSD). PSD can impact overall recovery, however treatment guidelines remain unclear. Usual care generally consists of antidepressants despite cognitive behavioural therapy (CBT) being a first-line treatment for depression. This evidence review aims to assess the effectiveness of CBT compared with antidepressants for treating PSD in adult stroke patients. Evidence searches of MEDLINE, PUBMED, The Cochrane Library, PsycINFO and NICE Evidence Search were conducted using strict search terms. The results were screened and appraised. A reference list search was carried out and included reviews with these results also screened and appraised. Appraisals used the AGREE II tool for guidelines and the CASP systematic review and randomised controlled trial (RCT) frameworks. Each stage was carried out by two independent reviewers, with disagreements resolved by a third reviewer. After applying inclusion and exclusion criteria, two guidelines, four reviews and one RCT were included in the synthesis. One review found CBT effective for treating PSD. Two reviews found CBT combined with antidepressants more effective than antidepressants alone. One review concluded CBT was ineffective for treating PSD. A single RCT found CBT more effective than antidepressants if PSD onset was nine months post-stroke, but PSD onset six months post-stroke was most effectively treated by antidepressants. Results for less than six months post-stroke were inconclusive. In conclusion, the findings of this evidence review suggest it is not possible to definitively conclude whether CBT is more or less effective than antidepressants. A combination of both is likely to be most effective. Lack of research means conclusions for clinical practice are difficult to draw. More research is needed before specific guidelines can be compiled.

INTRODUCTION

The World Health Organisation (WHO) defines stroke as a clinical syndrome characterised by "rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause apart from that of vascular origin". (1) Stroke is the fourth leading cause of death in the UK. (2) The long-term burden of stroke on survivors is just as significant: in 2016, stroke accounted for close to 20,000 age-specific years with lived disability per 100,000 in England. (3)

It is well-acknowledged that stroke can result in functional and physical decline. (4) Advances in the multidisciplinary team (MDT) approach to stroke aftercare, particularly physiotherapy, go some way towards addressing this issue. (5) However, the psychological effects of stroke, despite being seen in 30% of stroke patients, do not have such a recognised approach. (6)

An example of this is post-stroke depression (PSD). PSD can occur immediately or even years after a stroke and can be more debilitating for patients than the physical effects of stroke. (7) Additionally, PSD has the potential to seriously impede physical recovery due to its impact on motivation. (7)

The mechanism of PSD development is currently unclear, but it appears to be a combination of the direct physical effects of stroke on the brain and a psychological reaction to sudden and marked functional decline. (8) This ambiguity may account for the lack of recognised interventions for PSD, with the National Institute for Health and Care Excellence (NICE) stroke guidelines suggesting no clear pathway, stating instead to "Manage depression or anxiety in people after stroke who have no cognitive impairment in line with recommendations in depression in adults with a chronic physical health problem". (9)

In practice, lack of psychological practitioners within the stroke MDT often means specialised psychological treatment is not available, and the condition is poorly managed in the inpatient setting. (10)

Stroke patients still suffering from PSD after discharge are sometimes able to access general psychological support and cognitive behavioural therapy (CBT) through their general practitioner. CBT is the first-line treatment for depression in adults (11) and it is therefore thought that it may have some merit in treating PSD.

Evidently, PSD is an area in stroke rehabilitation which is underfunded and poorly understood. (8) There is limited knowledge into the best way to manage this condition, whether antidepressants, CBT, or a combination is most effective. The positive consequences for post-stroke patients of developing a clear and effective strategy for treating PSD could be extensive in both physical and psychological recovery.

Therefore, the aim of this evidence review is to assess the effectiveness of CBT compared with antidepressants for the treatment of PSD in adult stroke patients.

METHODS

Review Question

A population, intervention, comparator and outcome (PICO) framework was generated. This formed the basis of the review question: What is the effectiveness of cognitive behavioural therapy compared with antidepressants for the treatment of post-stroke depression in adult stroke patients?

The PICO framework was as follows:

Population: Adults who have had a stroke (according to the WHO definition) (1) and suffer from post-stroke depression, defined as depressive disorder due to another medical condition (i.e., stroke) (4, 12)
Intervention: CBT, defined as talking therapy to help change a patient's thinking and behaviour (13)
Comparator: Antidepressants
Outcome: Primary Outcome: Amelioration in depression (assessed by any validated depression rating scale)
Secondary Outcomes: Improvement in quality of life, improved functional ability

Literature Searches

A thorough literature search for guidelines, reviews and primary research studies was subsequently undertaken. Each of the steps outlined below were carried out by two independent reviewers with any disagreements resolved by a third reviewer.
Guidelines were searched for using NICE Evidence Search (Figure 1). Broad search terms (Table 1) were used because a scoping search revealed limited guidance on PSD. The search strategy is summarised in Figure 1. First, title/summary screening was undertaken, followed by a screen of full texts. Those meeting the inclusion criteria (Table 2) were then appraised using the AGREE II tool. (14)

Next, a review search was conducted using specific search terms (Table 1) using the following databases: MEDLINE, PUBMED, the Cochrane Library, and PsycINFO. Scoping searches revealed that including the search term 'antidepressant' would detrimentally limit the results as some papers used specific antidepressant names. It was therefore decided that to capture all relevant research, the use of antidepressants would form part of the inclusion criteria, instead of search terminology. More filters were added when searching PUBMED, such as 'meta-analysis' in addition to 'review', as the database uses filters and not limits. The search strategy used is demonstrated in Figure 2. Identified reviews were collated and duplicates were removed. Titles and abstracts were then screened to ensure the papers met inclusion and exclusion criteria. Next, a full text screen was undertaken. A reference list search was carried out on all included reviews. The Critical Appraisal Skills Programme (CASP) checklist for systematic reviews was used to critically appraise all included reviews. (15)

Finally, a search for primary research studies was completed using specific search terms (Table 1). The search was carried out on the following databases: MEDLINE, PUBMED, the Cochrane Library, and PsycINFO. A similar search strategy to the review search was carried out (Figure 2), with suitable papers being critically appraised using the CASP checklist for randomised controlled trials (RCTs). (16) One relevant RCT was identified through the search. (17) Despite being appraised in an included meta-analysis, (18) this study was re-evaluated by the current authors and is included in the results section below as it was the only paper to make a direct comparison between CBT alone and antidepressants alone, thus addressing the central review question.

Search Terms

Evidence searches on the databases listed above were carried out with the search terms and limits summarised in Table 1. The British English spellings of search terms were used, except for MeSH terms as the databases used the American English spelling. All PUBMED MeSH terms were automatically searched as both MeSH terms and keywords. See Appendix 1 for specific search terms used and results from each database.

Inclusion and Exclusion Criteria

The inclusion criteria applied to the guideline search were: English language guidelines, guidelines relevant to clinical practice, and guidelines that include recommendations for the treatment of PSD.

The inclusion criteria applied to the searches for reviews and primary research studies were: studies including patients who meet the review definition of stroke and the review definition of PSD, studies which evaluate CBT (according to this review's definition), and studies including an antidepressant comparator.

The exclusion criteria applied to the searches for reviews and primary research studies were: studies including patients under the age of 18.

RESULTS

Search Results

The search identified 2 guidelines, (19, 20) 3 narrative reviews, (21-23) 1 meta-analysis (18) and 1 RCT (17) meeting the inclusion criteria (see Figures 1 and 2). A reference list search returned no new papers. The results of identified papers are summarised in Table 2. Sample sizes were available for two out of the seven included literatures and were as follows: Wang et al (23 studies, 1972 participants), (18) Gao et al (2113 participants). (17)

Guidelines

There were no NICE guidelines identified. Two guideline documents were appraised using the AGREE-II tool: (14) the American Heart Association guidelines (19) for PSD and the Scottish Intercollegiate Guidelines Network (SIGN) (20) for stroke management.

The American Heart Association guidelines (19) stated that seven trials, (24-28) which investigated 775 individuals with PSD, suggested that "brief psychosocial interventions" may be useful in treating PSD. These seven trials were published in five research papers. (24-28) However, the guidelines did not comment on the concurrent use of antidepressants and there were few details about appraisal. Limitations recognised by the authors included small sample sizes and single-centre recruitment, so the trials were unlikely to be representative of a wider population. Due to the similar pattern of results demonstrated by the included studies, the authors concluded that psychosocial interventions show promise, but did not make any concrete recommendations.

The SIGN guideline published in 2010, (20) which addresses the management of patients after a stroke, stated that patients should be given antidepressants to treat their PSD. However, if the antidepressants did not work, the guidelines advised that patients should be considered for a talking-based therapy such as CBT. The SIGN guidelines relied on a Cochrane review of antidepressant and psychotherapy treatment for PSD to support their findings, (29) however, the studies included in this review had a high level of heterogeneity and the study types were not stated. As there was very little robust evidence of whether psychological therapies (including CBT) have efficacy in PSD treatment, the guidelines struggled to determine its usefulness.

Meta-analysis

One meta-analysis, Wang et al (18) was identified and appraised. A meta-analysis containing RCTs is the best available evidence according to the hierarchy of evidence; (30) therefore, this paper was appraised using the CASP systematic review checklist. (15) Wang et al evaluated whether CBT was more effective than standard care (seven RCTs), or whether CBT combined with an antidepressant was more effective than the antidepressant alone (14 RCTs) in treating PSD. (18) The results of the review demonstrated that both CBT alone and CBT combined with antidepressants were significantly more effective at reducing PSD than in the control groups (placebo, or antidepressant without CBT).

However, two other RCTs in this review had subjects in both the intervention (CBT) and control (placebo) groups who received antidepressants. There was no significant difference between the intervention and control groups, however these results may be swayed by some participants using antidepressants in the intervention/control groups. It would have been useful to see a baseline characteristics table to assess whether this would have had an effect. These results are shown in Table 3.

CBT was also shown to have a positive impact on anxiety, activities of daily living and neurological functional deficient as secondary outcomes.

Wang et al had a clearly defined PICO (P = patients with PSD according to any criteria, I = CBT alone or CBT with

Table 1

Search terms used to generate search results for guidelines, systematic reviews and primary research studies

Search	Database	Search Terms (MeSH terms underlined, keywords = normal type)	Limits/Filters Applied
Guidelines	NICE Evidence Search	Post-stroke Depression	Guidance
Reviews	MEDLINE (1946 – current day)	(Stroke OR Brain Ischaemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accident) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioural Therapy or Counseling or Cognitive Behaviour Therapy or CBT)	Limits Review English language
	PUBMED	(Stroke OR Brain Ischaemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accident) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioural Therapy OR Counseling OR Cognitive Behaviour Therapy OR CBT)	Filters Review Meta-analysis Systematic reviews English language
	Cochrane Library	(Stroke OR Brain Ischaemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accident) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioural Therapy OR Counseling OR Cognitive Behaviour Therapy OR CBT)	Limits Reviews
	PsycINFO (1967 – current day)	(Stroke OR Brain Ischaemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accidents) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioural Therapy OR Counseling OR Cognitive Behaviour Therapy OR CBT)	Limits Systematic reviews Literature reviews Meta-analysis English language
Primary research studies	MEDLINE (1946 – current day)	(Stroke OR Brain Ischemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accident) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioral Therapy or Counseling or Cognitive Behaviour Therapy or CBT)	Limits Randomized controlled trial English language
	PUBMED	(Stroke OR Brain Ischaemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accident) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioural Therapy OR Counseling OR Cognitive Behaviour Therapy OR CBT)	Filters Randomized controlled trial English language
	Cochrane library	(Stroke OR Brain Ischaemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accident) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioural Therapy OR Counseling OR Cognitive Behaviour Therapy OR CBT)	Limits Trials
	PsycINFO (1967 – current day)	(Stroke OR Brain Ischaemia OR Cerebral Haemorrhage OR Cerebrovascular Event OR Cerebrovascular Accidents) AND (Depression OR Post-stroke depression) AND (Cognitive Behavioural Therapy OR Counseling OR Cognitive Behaviour Therapy OR CBT)	Limits Clinical trial English language

Figure 1

Flowchart demonstrating the search strategy for guidelines

Flowchart includes the number of guidelines included and excluded at each

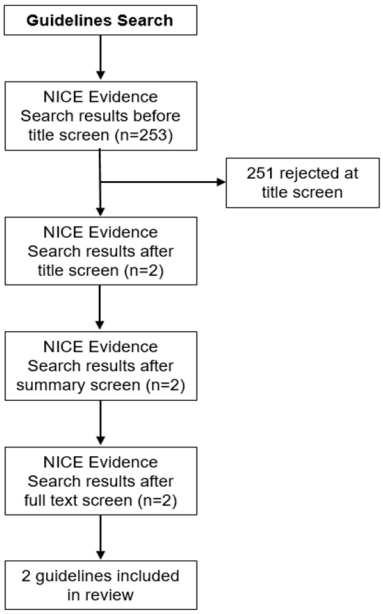

Figure 2

Flowchart demonstrating the search strategy for reviews and primary research

Flowchart includes the number of primary research studies and reviews included and excluded at each stage. Abbreviations: n = number of articles, PRS = primary research study, R = review

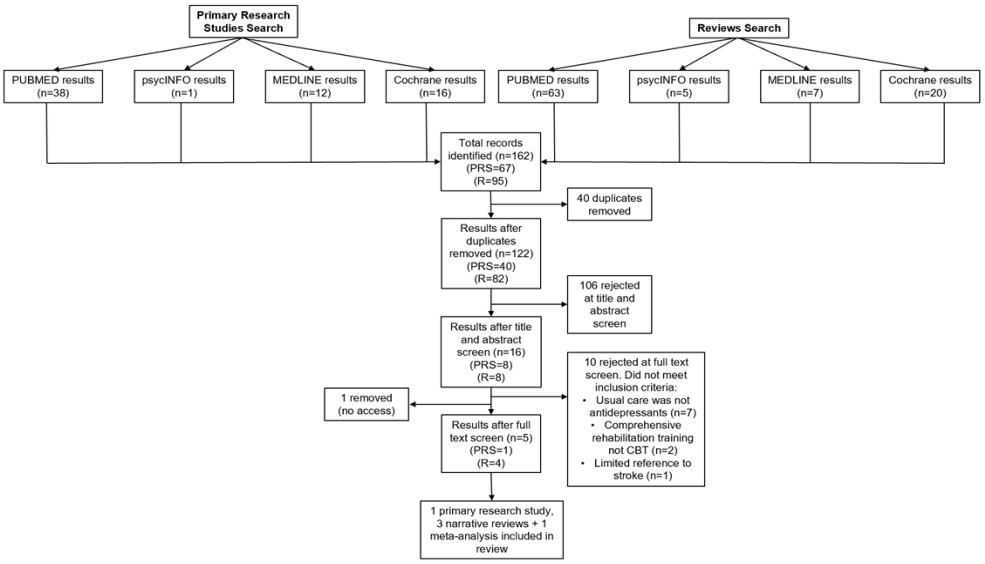

Table 2

Summary of Results of Included Literature

Authors	Study type	Setting	Year of publication	Results
Towfighi et al.	Guideline	American guidelines	2017	Brief psychological interventions may be useful in PSD treatment
Scottish Intercollegiate Guidelines Network	Guideline	Scottish guidelines	2010	Antidepressants were first-line PSD treatment and talking based therapy was second-line
Wang et al.	Meta-analysis	British and Chinese databases searched	2018	Both CBT alone and CBT combined with antidepressants were significantly more effective than placebo or antidepressants alone
Kneebone et al.	Narrative review	British review of international literature	2000	RCTs investigating CBT or other forms of psychotherapy found CBT was either not effective or showed "borderline statistical significance"
Robinson et al.	Narrative review	American review of international literature	2016	CBT alone was found to be ineffective
Hadidi et al.	Narrative review	American review of international literature	2017	CBT alone was found to be ineffective. A combination of antidepressants and problem based therapy was better than antidepressants alone
Gao et al.	Randomised controlled trial	Chinese RCT conducted in the outpatient setting	2017	Antidepressants were effective for PSD when it develops 6-9 months post-stroke, and CBT was effective >9 months post-stroke

Table 3

Results of the Wang et al meta-analysis (18)

Subgroup	Standardized Mean Difference [95% confidence intervals]	P-value	Number of RCTs
CBT alone	-0.76 [-1.22 to -0.29]	0.001	7
CBT with antidepressant	-0.95 [-1.20 to –0.71]	<0.0001	14
CBT with some participants on antidepressants	-0.20 [-0.53 to 0.13]	Not given but authors state there was no significant difference	2
Overall	-0.83 [-1.05 to -0.60]	<0.001	23

antidepressants, C = placebo or the same antidepressant as with the CBT group, O = efficacy) and comprehensive search strategy including English and Chinese databases. (18) The search was carried out by three independent investigators. The inclusion of non-English language papers from the Chinese databases reduces the risk of publication bias, as demonstrated by the Egger's regression test that found no statistically significant evidence of publication bias for the overall effect of CBT on PSD.

The search identified 23 applicable RCTs, which were then divided into the three subgroups shown in Table 3. They included a total sample size of 1,972 participants, with 21 of the studies (sample size 1,829) carried out on a Chinese population.

The quality of the studies was assessed using both the Cochrane Risk of Bias Tool and the Jadad scale. A study with a Jadad score of 3 or more was said to be of high quality; less than 3 indicated low quality. Only nine of the studies were found to be of high quality according to this scale. Reasons for the low quality of studies were secondary to the methods of randomisation being unclear in 15 studies, and poor reporting of compliance rates for the intervention. The authors also used I2 statistics to measure heterogeneity, with an I2 of 82% indicating significant heterogeneity between the studies. Although the results were statistically significant, the heterogeneity could mean that it was inappropriate to combine the different studies' results, as the different studies used varied methods and sample sizes. This was a common theme in the literature found.

Narrative Reviews

Kneebone et al, (21) Robinson et al, (22) and Hadidi et al (23) carried out literature reviews to collate information on psychological interventions in PSD. Most of the research included in these papers were RCTs, the highest quality primary research for interventions, according to the hierarchy of evidence. (21, 30) Despite RCTs being included, meta-analysis was not possible, due to the heterogeneity of the studies. For example, many different types of psychological interventions were assessed in each review, such as ecosystem-focussed therapy or problem-solving therapy. Therefore, despite these reviews containing high-quality primary research, the Wang et al meta-analysis is the highest quality evidence included in this evidence review. (18, 30)

Kneebone et al concluded that although CBT represented a promising area of future research, more investigations and high-quality RCTs were needed to fully establish its effect on PSD. (21) More recent reviews from Robinson et al and Hadidi et al concluded that CBT alone was ineffective. (22, 23) However, Hadidi et al found that a combination of problem-solving therapy (falling under this review's definition of CBT) and antidepressants was more likely to be effective than antidepressants alone. (23) These three reviews did not have specific PICO frameworks or focused questions, (21-23) but they all had clear aims: to gather all relevant information on psychological interventions (Kneebone et al) (21) and "nonpharmacological interventions" (Hadidi et al). (23) The purpose of the Robinson et al paper was to investigate antidepressants. (22) However due to their non-specific search terms, including "post stroke depression AND trial", (22) it also included studies on psychological interventions, which were discussed by the authors, hence its inclusion in this review. All reviews searched medical databases such as MEDLINE and psychology databases such as PsycINFO. They carried out reference searches and Hadidi et al reported their appropriate inclusion and exclusion criteria, for example, qualitative studies were excluded, and the patients included were required to have depressive symptoms. (23. However, there was no universal scale used by Hadidi et al to assess these symptoms. (23)

All three reviews included papers relevant to their aim. Kneebone et al included case studies and uncontrolled trials, (21) making it more likely that results could have been affected by confounders and bias, such as selection bias. The inclusion of such studies was recognised as a limitation by the authors. However, as this review was published in 2000 when there was less information available regarding the mental health of stroke survivors, these preliminary papers provide a useful introduction to this topic.

None of the reviews demonstrated a consistent appraisal of the quality of papers included, and full information on some of the studies, such as setting and the demographics of the population, was not available, therefore it was difficult to fully assess the quality of the paper.

The quality of case studies on CBT, featured in Kneebone et al. (21) were not evaluated and it was simply stated they resulted in an improvement in mood. The authors assessed the quality of the uncontrolled studies and concluded they were poor quality preliminary studies due to the lack of a control group. The quality of the few RCTs included was not formally assessed, there was no detail of randomisation or blinding given and most had small sample sizes. The RCT results showed that CBT or other forms of psychotherapy were not effective or demonstrated "borderline statistical significance", (21) however the authors emphasised the poor quality of these papers and therefore concluded that more RCTs were needed.

Incomplete details were given on the RCTs featured in Robinson et al. (22) but it was made clear that RCTs evaluating problem-solving therapy had small sample sizes and high dropout rates, increasing the chance of confounding factors and attrition bias affecting results. It was not stated if intention-to-treat analysis was used. Out of these three reviews, Hadidi et al. had considered most thoroughly the quality of papers included. (23) Although there was limited information about how this was carried out, the authors did discuss how the rigour of the studies varied, considering sample size (ranging from 14-411), time after stroke (48 hours to 5 years) and differences in baseline characteristics (for example variation in depression scores between groups). Hadidi et al., (23) similarly to the other reviews, did not present results as a meta-analysis. This was not justified by the authors, but as mentioned previously, was likely due to the heterogeneity between studies. Only one RCT explicitly stating CBT as the intervention was included. (31) The authors recognised the limitations of using this study, for example the CBT practitioner was not fully trained, and possible cognitive impairment was not considered by the RCT researchers.

Considering all three narrative reviews, it is difficult to evaluate whether the results are applicable to the local population, due to the poor quality and lack of information on the participant characteristics. All three reviews concluded that CBT is a promising area of research.

Primary Study (RCT)

One primary study, an RCT by Gao et al., (17) was found and appraised using the CASP RCT checklist. (16) As stated previously, this is the only relevant RCT that was found in the literature search that directly compared CBT alone to antidepressants alone, thus making it the most suitable study found for the review question. For this reason, it was covered in this review despite already being included in the Wang et al. meta-analysis (18). RCTs are not considered as robust as "filtered information" (30) such as meta-analyses and guidelines, therefore it is important to reflect on these results in combination with the literature appraised above. Gao et al. examined the effectiveness of CBT treatment stratified by time taken for PSD to develop after stroke. (17) This was not quantified in the Wang et al. meta-analysis. (18)

Gao et al. took patient groups at discharge and at 3, 6 and 9 months post-discharge following a stroke, and then split these groups into A, B and C as follows: Group A had placebo tablets and placebo psychological intervention, Group B had active citalopram antidepressant tablets and placebo psychological intervention, and Group C had placebo tablets and active CBT. (17)

It was a single-blind trial - the patients were blinded to the treatment they were receiving. They then followed these patients up for 3 months and used the Hamilton Depression Rating Scale (HAM-D) and the Bech-Rafaelsen Melancholia Scale (MES) to measure depressive symptoms.

The results of the study, when time stratification was not considered, showed no significant differences in the HAM-D scores between groups A, B and C. The only significant difference in MES scores was a lower score (fewer depressive symptoms) in Group B compared to Group A ($p=0.02$). This suggests antidepressants could be more effective than placebo tablets, whereas CBT is not significantly different to placebo psychological intervention at reducing depressive symptoms. These results contrast with Wang et al., (18) which showed that CBT alone was significantly more effective compared to placebo. It could be said that the results from Wang et al. are more valid as systematic reviews are higher in the hierarchy of evidence than RCTs. (18, 30) Furthermore, Gao et al. was not significantly highly weighted within the meta-analysis. (17, 18) However, Gao et al. was only one of two studies included in the meta-analysis with the highest possible Jadad score of 5, (17) and therefore is deemed to be of higher quality than the other RCTs in Wang et al. (18). This could mean that the meta-analysis results may be produced from RCTs with a higher risk of bias, and the Gao et al. results are more likely to be reliable.

Importantly for this review question, Gao et al. demonstrated that, without stratification by time, there was no significant difference in the depression rating scores between the groups receiving CBT alone (Group C) and the antidepressant alone (Group B). (17) However, when time stratification was considered, there was a different picture of results. At 6 months post-discharge, Group B had significantly lower HAM-D/MES scores when compared to Group A, and Group C showed no significant decrease in score in comparison to Group A. This could suggest that antidepressants (Group B) are more effective at reducing depressive symptoms than CBT (Group C) when treatment is initiated 6 months post-discharge. Furthermore, at 9 months post-discharge, Group C showed significantly lower MES scores compared to Group A, and Group B showed no significant decrease in comparison to Group A. These results demonstrate that CBT (Group C) may be more effective than antidepressants (Group B) when these symptoms develop later, when CBT treatment is initiated at 9 months post-discharge.

Gao et al. had a clearly focused PICO, appropriate randomisation with all groups having similar baseline characteristics and detailed follow-up of patients and drop-outs, with reasons provided. (17) However, some limitations included that there was no mention of whether participants were analysed with an intention-to-treat analysis. If not, this could lead to attrition bias and selection bias, due to loss of randomisation. Also, sample sizes were small, especially when split into time-stratified groups, therefore reducing the power of detecting significant differences between the subgroups.

DISCUSSION

The aim of this review was to assess the effectiveness of CBT compared to the effectiveness of antidepressants for the treatment of adults with PSD. The main findings suggest a mixture of results regarding the effectiveness of CBT, however there is evidence that this therapy could have a larger role in PSD treatment than it currently does. The available evidence varies considerably in methodological quality and so further research into the treatment for PSD is needed.

It should be considered that one of the reasons for lack of research into the treatment of PSD is a lack of understanding of the development of PSD. (8) The question remains over whether PSD results from the direct physical effects of stroke on the brain, a psychological reaction to the patient's own sudden and marked functional decline, or, perhaps more likely, a combination of both causes. Should this important question be answered, our understanding of PSD will improve and therefore this may lead to more research into PSD treatment. For example, it is not yet understood why CBT appears to be more effective in some studies than antidepressants. A theory for this could be that the possible biological mechanism of PSD does not align with the mechanism of action of antidepressants. However, we will not know if this is the case until future research on the development of PSD becomes available.

Furthermore, considering evidence around treating depression thought to be a consequence of other chronic illnesses may enable us to identify further treatment options to explore.

However, the possible direct biological mechanism of PSD means that a direct comparison to depression in other chronic illnesses may be unhelpful. This further emphasises the need for research into PSD development.

It has been identified that if a patient was to be given CBT as a PSD treatment, then this CBT should be individually adapted to suit different patient needs. (8) This is because PSD affects individuals differently such as effects on motivation and sleep, and a universal CBT protocol would not consider these differences. Qualitative research could help to understand the impact these aspects have on patients as individuals, where current scoring systems may fail to grasp the range of emotions patients feel in such a hard time.

This review has highlighted that there are prominent gaps in the research of treating PSD. One possible reason for this lack research could be societal attitudes towards mental ill-health. As mental illness is not defined by physical attributes, it is said that society in general finds it harder to accept that mental health is as important as physical health. (32) A 2011 NHS report about attitudes to mental illness found that 23% of the participants did not agree that mental illness was akin to physical illness. (32) These beliefs are reflected in funding differences between physical and mental illness. (33) This could explain the lack of research on the topic of PSD treatment, particular in the context of the sometimes-life-changing physical difficulties stroke can cause.

To address gaps in the knowledge of PSD, future RCTs should be conducted with a culturally diverse study population, mirroring that of the UK. This is of particular importance because most current evidence on this topic area was conducted on mainly Chinese populations. (17, 18) CBT as a treatment focuses on innate beliefs meaning participants from different cultures with different attitudes towards mental health are likely to respond differently to it. Hence it may not be appropriate for such studies to form the basis of UK national treatment guidelines. Understanding the issue within the context of the UK population to form relevant guidelines could provide public health benefit, given that the disability burden post-stroke is so high in the UK.

Changes in the methodology of current studies could help produce results more applicable to medical practice. High-quality RCTs directly comparing antidepressants to individually tailored CBT would be particularly useful for compiling new NICE guidelines. Continuing to research the effect of treatments started at different time periods post-stroke would be more reflective of clinical practice as patients are likely to present with depression at various times after their stroke. The emergence of such research would allow future clinicians to fully evaluate whether CBT is a worthwhile and possibly more effective treatment for PSD than antidepressants for certain patients.

Furthermore, changes in methodology could address challenges in conducting RCTs in this population group. Patients struggling with the most severe effects of stroke and post-stroke depression may be less likely to consent to participating in a study. The potential participation bias resulting from this could be reduced in future studies by controlling for severity of stroke and expected rehabilitation time. Attrition rates in those most affected by their stroke may also be higher and this is something to explore in the future, to ensure validity of results. In terms of impact on current practice, despite this review finding that there is not enough evidence for making definitive clinical guidelines, it should allow clinicians to feel more confident in suggesting CBT as a treatment option for PSD if they feel it is right for their patient. This may encourage more doctor-patient discussion and allow patients to be more involved in treatment decisions.

Beyond the boundaries of this review lies the question of how the availability, cost and patient acceptability of antidepressants and CBT influence a clinician's treatment decision, consequently affecting a patient's overall functional recovery from PSD. This influence on recovery has implications on the financial aspect of managing PSD. Improvements in both the psychological and physical effects of PSD are likely to decrease burden of care, which is usually high in post-stroke patients, allowing NHS resources to be used more efficiently.

CONCLUSION

To conclude, the treatment of PSD is an important yet under-funded area of research despite being a common consequence of a stroke. The findings of this review suggest the evidence supporting the use of CBT versus antidepressants for the treatment of PSD is inconclusive, which may in part be due to low levels of methodological quality. In practice, a combination of pharmacological and CBT treatment is likely to be most effective and this warrants further research. Future high-quality RCTs that include culturally diverse patient populations and clinically relevant interventions, comparisons and outcomes are needed to address this research question.

REFERENCES

1. World Health Organisation international classification of diseases. 9th ed. Geneva: World Health Organisation; 1965.

2. Office for National Statistics. Deaths registered in England and Wales (series DR). London: Office for National Statistics; 2017 [accessed 30 April 2019]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregisteredinenglandandwalesseriesdr/2017.

3. GOV.UK. Chapter 3: trends in morbidity and risk factors. London: Crown Copyright; 2018 [accessed 30 April 2019]. Available from: https://www.gov.uk/government/publications/health-profile-for-england-2018/chapter-3-trends-in-morbidity-and-risk-factors.

4. Stroke Association. A New Era for Stroke Our campaign for a new national stroke strategy. London: Stroke Association; 2016 [accessed 30 April 2019]. Available from: https://www.stroke.org.uk/sites/default/files/anefs_report_web.pdf.

5. Stroke Association. Physiotherapy after stroke. London: Stroke Association; 2019 [accessed 30 April 2019]. Available from: https://www.stroke.org.uk/sites/default/files/physiotherapy_after_stroke.pdf.

6. Paolucci S. Epidemiology and treatment of post-stroke depression. Neuropsychiatr Dis Treat. 2008;4(1):145-54.

https://doi.org/10.2147/NDT.S2017

PMid:18728805 PMCid:PMC2515899

7. Stroke Association. Depression – National Stroke Association. London: Stroke Association; 2019. Available from: https://www.stroke.org/we-can-help/survivors/stroke-recovery/post-stroke-conditions/emotional/depression.

8. Broomfield NM, Laidlaw K, Hickabottom E, Murray MF, Pendry R, Whittick JE, et al. Post-Stroke Depression: The Case for Augmented, Individually Tailored Cognitive Behavioural Therapy. Clin Psychol Psychother. 2011;18:202-217.

https://doi.org/10.1002/cpp.711

PMid:20632301

9. National Institute for Health and Care Excellence. Guidance | Stroke rehabilitation in adults | Guidance. London: NICE; 2019 [accessed 30 April 2019]. Available from: https://www.nice.org.uk/guidance/cg162.

10. National Institute for Health and Care Excellence. NHS Improvement – Stroke | Psychological care after stroke. London: NICE; 2019 [accessed 30 April 2019]. Available from: https://www.nice.org.uk/media/default/sharedlearning/531_strokepsychologicalsupportfinal.pdf.

11. National Institute for Health and Care Excellence. Guidance | Depression in adults: recognition and management | Guidance. London: NICE; 2018 [accessed 30 April 2019]. Available from: https://www.nice.org.uk/guidance/cg90.

12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, Virginia: American Psychiatric Association; 2013.

13. NHS. Cognitive behavioural therapy (CBT). London: NHS; 2016 [accessed 29 April 2019]. Available from: https://www.nhs.uk/conditions/cognitive-behavioural-therapy-cbt.

14. AGREE Next Steps Consortium. The AGREE II Instrument. Hamilton, Ontario: AGREE Enterprise Project; 2013 [accessed 29 April 2019]. Available from: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf.

15. Critical Appraisal Skills Programme. CASP Systematic Review Checklist. Oxford: CASP UK; 2018 [accessed 29 April 2019]. Available from: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf.

16. Critical Appraisal Skills Programme. CASP Randomised Controlled Trial Checklist. Oxford: CASP UK; 2018 [accessed 29 April 2019]. Available from: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Randomised-Controlled-Trial-Checklist-2018_fillable_form.pdf.

17. Gao J, Lin M, Zhao J, Bi S, Ni Z, Shang X. Different interventions for post-ischaemic stroke depression in different time periods: a single-blind randomized controlled trial with stratification by time after stroke. Clin Rehabil. 2017;31(1):71-81.

https://doi.org/10.1177/0269215515626232

PMid:26817808

18. Wang SB, Wang YY, Zhang QE, Wu SL, Ng CH, Ungvari GS, et al. Cognitive behavioural therapy for post-stroke depression: A meta-analysis. J Affect Disord. 2018;235:589-596.

https://doi.org/10.1016/j.jad.2018.04.011

PMid:29704854

19. Towfighi A, Ovbiagele B, El Husseini NE, Hackett ML, Jorge RE, Kisella BM et al. Poststroke Depression: A Scientific Statement for Healthcare Professionals From the American Heart Association. Stroke. 2017;48:30-43.

https://doi.org/10.1161/STR.0000000000000113

PMid:27932603

20. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. Edinburgh: SIGN; 2010 [accessed 30 April 2019]. Available from: https://www.sign.ac.uk/assets/sign118.pdf.

21. Kneebone II, Dunmore E. Psychological management of post-stroke depression. J Clin Psychol. 2000;39:53-65.

https://doi.org/10.1348/014466500163103

PMid:10789028

22. Robinson RG, Jorge RE. Post-Stroke Depression: A Review. Am J Psychiatry. 2016;173(3):221-231.

https://doi.org/10.1176/appi.ajp.2015.15030363

PMid:26684921

23. Hadidi NN, Huna Wagner RL, Lindquist R. Nonpharmacological Treatments for Post-Stroke Depression. An Integrative Review of the Literature. Res Gerontol Nurs. 2017;10(4):182-195.

https://doi.org/10.3928/19404921-20170524-02

PMid:28556875

24. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. Cochrane Database Syst Rev. 2008;4.

https://doi.org/10.1002/14651858.CD003437.pub3

PMid:18843644

25. Mitchell PH, Veith RC, Becker KJ, Buzaitis A, Cain KC, Fruin M. Brief Psychosocial–Behavioral Intervention With Antidepressant Reduces Poststroke Depression Significantly More Than Usual Care With Antidepressant. Living Well With Stroke: Randomized, Controlled Trial. Stroke. 2009;40(9):2073-3078.

https://doi.org/10.1161/STROKEAHA.109.549808

PMid:19661478 PMCid:PMC2777736

26. Kirkness CJ, Cain KC, Becker KJ, Tirschwell DL, Buzaitis AM, Weisman PL. Randomized trial of telephone versus in-person delivery of a brief psychosocial intervention in post-stroke depression. BMC Res Notes. 2017;10(1):500.

https://doi.org/10.1186/s13104-017-2819-y

PMid:29017589 PMCid:PMC5633890

27. Thomas SA, Walker MF, Macniven JA, Haworth H, Lincoln NB. Communication and Low Mood (CALM): a randomized controlled trial of behavioural therapy for stroke patients with aphasia. Clin Rehabil. 2013;27(5):398-408.

https://doi.org/10.1177/0269215512462227

PMid:23059701 PMCid:PMC3652643

28. Alexopoulos GS, Wilkins VM, Marino P, Kanellopoulos D, Reding M, Sirey JA. Ecosystem focused therapy in poststroke depression: a preliminary study. Int J Geriatr Psychiatry. 2012;27(10):1053-60.

https://doi.org/10.1002/gps.2822

PMid:22249997 PMCid:PMC3361524

29. Hackett ML, Anderson CS, House A, Halteh C. Interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2008;3.

https://doi.org/10.1002/14651858.CD003689.pub3

PMid:18646094

30. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. BMJ Evidence-Based Medicine. 2016;21:125-127.

https://doi.org/10.1136/ebmed-2016-110401

PMid:27339128 PMCid:PMC4975798

31. Lincoln N, Flannaghan T. Cognitive behavioural psychotherapy for depression following stroke: A randomized controlled trial. Stroke. 2003;34(1):111-115.

https://doi.org/10.1161/01.STR.0000044167.44670.55

PMid:12511760

32.The NHS Health and Social Information Centre. Attitudes to Mental Illness – 2011 survey report. London: NHS; 2011 [accessed 6 May 2019]. Available from: https://files.digital.nhs.uk/publicationimport/pub00xxx/pub00292/atti-ment-illn-2011-sur-rep.pdf.

33. National Institute of Health and Care Excellence – Clinical Knowledge Summaries. Depression: What is the prognosis? London: NICE; 2015 [accessed 2 May 2019]. Available from: https://cks.nice.org.uk/depression#!backgroundSub:5.

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Original Research

The role of the glucocorticoid receptor in anti-hormone resistance in breast cancer

ORIGINAL RESEARCH

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ABSTRACT

Background: Approximately 75% of all breast cancer diagnoses are oestrogen receptor (ER) positive. In such ER positive subtypes, anti-hormones such as fulvestrant and tamoxifen are a mainstay therapy. However, the efficacy of these agents is severely limited by subsequent development of resistance. The glucocorticoid receptor (GR) has been implicated as a possible resistance mechanism owing to transcription of pro-proliferative and anti-apoptotic genes in breast cancer cells. A similar contributory role to resistance has also been observed in anti-hormone resistant prostate cancer suggested by increased GR expression and tumour progression. These associations are of particular concern given the use of glucocorticoids as an adjuvant treatment in breast cancer. This research aims to assess the impact of fulvestrant and tamoxifen on GR expression in the anti-hormone treated and resistant MCF-7 ER positive breast cancer cell line.

Methods: mRNA and protein expression of the GR were investigated by reverse transcription polymerase chain reaction and Western blotting respectively, in the ER positive MCF-7 breast cancer cell line. Expression in wild-type cells was compared to cells following short-term (7 day) oestrogen (1nM) and fulvestrant (100nM) treatment, and in cells with acquired resistance to fulvestrant and tamoxifen.

Results: Both fulvestrant treated and resistant MCF-7 cells exhibited increased GR mRNA and protein expression which was statistically significant in resistant cells at the protein ($p=0.0345$) but not mRNA level. Tamoxifen-resistant cells also exhibited increased GR protein expression.

Conclusion: These data demonstrate up-regulation of the GR during treatment with, and following acquisition of resistance to, the anti-hormone fulvestrant. This supports potential for increased expression of GR-regulated pro-survival genes in resistance, indicating a potential role for the GR in anti-hormone resistant breast cancer. Further research into this area is warranted to improve clinical outcomes.

BACKGROUND

Breast Cancer

Worldwide, breast cancer is the most common malignancy in females, and a significant health burden, accounting for 627,000 deaths in 2018. (1) Approximately 75% of breast cancers express or overexpress the ER isoform designating them ER positive (2-4) and sensitive to the proliferative drive of oestrogens. (2) The central role played by oestrogen in breast cancer progression has denoted anti-oestrogens a mainstay in the therapeutic armamentarium against ER positive disease. However, the clinical utility of these agents is confounded by acquisition of resistance in approximately 40% of initially responsive adjuvant patients, (5) and 25% of all breast cancer cases. (6)

Availability of anti-oestrogens has nonetheless revolutionised disease prognosis. For example, the selective oestrogen receptor modulator (SERM) tamoxifen contributed to the nearly 50% annual reduction in breast cancer recurrence and 30% survival improvement observed in the last 20 years. (6) However, as a competitive inhibitor of the ER, (7) tamoxifen retains the potential to function as an agonist, (8) as observed in bone and endometrial tissue. (9) These experiences prompted development of newer endocrine agents, such as aromatase inhibitors, which interfere with oestrogen production by the aromatase enzyme, and selective oestrogen receptor down-regulators (SERDs) such as fulvestrant (Faslodex ®). Fulvestrant (Faslodex ®) is recommended by the National Institute for Health and Care Excellence (NICE) in post-menopausal women with locally advanced or relapsed metastatic ER positive breast cancer, who have previously been treated with aromatase inhibitors, or have developed treatment resistance. (10) In contrast to tamoxifen, fulvestrant is a pure ER antagonist, devoid of the adverse pharmacology and sequelae reflective of tamoxifen's agonistic potential. (11) Mechanistically it exhibits widespread actions including inhibition of ER binding oestrogen and co-activator proteins, decreased nuclear translocation of ligand-bound ER, reduced capability of ER:ERE interactions, and inhibition of ER dimerisation by induction of receptor conformational changes. (8) It is also unique in that it enhances ER degradation. (8) Hence, by down-regulating the ER, fulvestrant abrogates transcription of oestrogen-regulated target genes by both inhibiting oestrogen-dependent signaling and preventing oestrogen-independent ER activation. (7,12)

Mechanisms of acquired anti-hormone resistance

Gradual loss of endocrine responsiveness occurs in the majority of patients treated with endocrine agents within 2-3 years. (4) Loss of ER expression has been postulated as a causative factor, although this appears unlikely given the majority of resistant tumours retain a functional ER, and demonstrate responsiveness to subsequent endocrine therapies. (13) An alternative hypothesised mechanism is interference mediated by other receptors. In particular, growth factor receptors such as human epidermal growth factor receptor 2 (HER2) have been extensively studied and as such established a precedent for receptor cross-talk in the induction of anti-hormone resistance. (14) However, since concomitant HER2 blockade with monoclonal antibodies fails to appease resistance development, (15) involvement of other receptors is indicated.

Recent studies have implicated nuclear steroid hormone receptors such as the glucocorticoid receptor (GR). Indeed, increased GR expression has been associated with anti-hormone resistance and tumour progression in prostate cancer, another predominantly hormone driven malignancy. (16) Similarly, in ER-negative breast cancer one study demonstrated that high GR expression is related to poor prognosis and increased relapse rates, (17) a significant finding given mechanistically fulvestrant generates an ER-negative cancer, particularly when resistance develops. (8) There is however a paucity of data investigating the role of the GR in ER-positive breast cancer which this study aims to address.

The GR in breast cancer

The anti-inflammatory properties of glucocorticoids (GCs), such as dexamethasone, position them an attractive and commonly used agent in breast cancer (18,19) which is potentially concerning if the GR is implicated in resistance as we hypothesise. However, this benefit appears to be cell-type-specific, (20) with anti-apoptotic functioning observed in mammary epithelial cells. (20,21) For example, dexamethasone treatment increases expression of the well-established anti-apoptotic, pro-proliferative gene serum-and-glucocorticoid-inducible-kinase-1 (SGK-1). (21) Significantly, SGK-1 overexpression has recently been cited as causal in anti-hormone resistance in prostate cancer (22) and found to abrogate apoptosis in mammary epithelial cells. (23) Similarly, dexamethasone induces up-regulation of the anti-apoptotic phosphatase enzyme MAPK phosphatase-1 (MKP-1). (24) Overexpression of MKP-1/DUSP-1 has been documented in breast and prostate carcinomas (24) and also ovarian cancer where it is associated with reduced progression free survival. (25) Such a pro-survival role for the GR in breast cancer is further supported by investigations of xenograft tumours of mice given systemic GCs, demonstrating increased mRNA expression of both SGK-1 and MKP-1, in addition to other anti-apoptotic genes. (24) Taken together, this evidence strongly implicates GR-regulated genes as mediators of breast tumour cell survival and suggests a role for the GR in the acquisition of endocrine resistance. This has particularly concerning implications regarding dexamethasone use in breast cancer patients.

Aims

The project evaluates the hypothesis that fulvestrant resistant ER-positive breast cancer cells display increased GR expression which theoretically would result in up-regulation of pro-survival genes, evidencing a clear role for the GR in the acquisition of anti-hormone resistance in breast cancer. The expression profile of the GR will be evaluated in ER-positive MCF-7 breast cancer cell line and compared between wild-type, oestrogen-treated, fulvestrant-treated, fulvestrant-resistant and in certain cases tamoxifen-resistant cells. This cell line was chosen as the ER-positive subtype is representative of approximately 70% of breast cancers seen clinically. (2-4)

METHODS

Cell culture and lysis

Oestrogen-receptor positive MCF-7 (AstraZeneca Pharmaceuticals, Macclesfield, UK) wild-type cells were grown and maintained in 5% Carbon dioxide, at 37°C, in red RPMI-1640 medium, containing Penicillin-streptomycin (10IU/ml-10µg/ml), Fungizone ® (amphotericin B, 2.5µg/ml) and 5% foetal calf serum (FCS).

Cultured wild-type cells were incubated for 24 hours in phenol red-free RPMI containing L-glutamine (200nM), 5% FCS, and antibiotics. Cells were then incubated for 7 days in media containing either oestradiol (1nM in ethanol), fulvestrant (100nM in ethanol), or media alone, producing 7-day-oestrogen treated, 7-day-fulvestrant-treated and control/wild-type cells respectively. The influence of lengthened anti-hormone exposure, as experienced in clinical practice, was investigated using fulvestrant and tamoxifen resistant MCF-7 cells. Such cells were generated by culturing wild-type MCF-7 cells in white RPMI media containing inactivated FCS and fulvestrant (Faslodex ®, 100nM) or 4-hydroxytamoxifen (100nM) respectively, for a minimum 6-month period.

Cultured cells were then lysed following three washes with phosphate buffered saline (PBS) by exposure to Halt Protease and Phosphatase Inhibitor Cocktail and ice-cold lysis buffer (Appendix A). Lysis product was transferred to eppendorfs, centrifuged (13 000 RPM, 4°C, 15 minutes), and stored at -20°C.

RNA isolation, amplification and detection

RNA samples were extracted from culture growing cells using a Tri® Reagent RNA Isolation Kit (Sigma-Alrich, Gillingham, UK). Absorbance of samples (1 in 200 dilutions) was measured using a CECIL CE 2041 spectrophotometer (Cecil Instruments, Cambridge, UK) at 260 and 280nm to determine total concentration.

The instability of isolated RNA demands it be reverse transcribed into relatively stable complementary DNA (cDNA) prior to amplification with Polymerase Chain Reaction (PCR). As such, 1µg of RNA sample and 11µl of RNA mastermix (Appendix B) were mixed in a sterile eppendorf and then denatured at 95°C for 5 minutes in a PCR thermal cycler (Techne TC-3000X, Bibby Scientific Ltd., Stone, UK). M-MLV reverse transcriptase and RNAase inhibitor (Fisher, UK) were added to the Eppendorf and the mixture reverse transcribed in the above machine (parameters in Appendix B) to form cDNA (stored at -20°C).

PCR was used to amplify small amounts of specific GR cDNA fragments using primer pairs (sequences in Appendix B). As with Western blotting, actin was used for control purposes. 0.5µl of cDNA from each treated cell sample was added to a PCR master-mix solution (Appendix B) to yield 4 samples: MCF-7 control (wild-type), MCF-7 oestrogen-treated, MCF-7 fulvestrant-treated and master-mix control (no cDNA), the latter to check for contamination. After centrifugation, samples were placed in a thermocycler at varying cycle numbers and parameters (Appendix B) determined by experimental optimisation. 7µl of each PCR product mixed with 5 µl of loading buffer (Appendix B) were loaded into the wells of a 2% agarose gel (Appendix B) containing RedSafe Nucleic Acid staining dye. The gel was run at 100V for 30 minutes using a Bio-Rad PowerPac. Once run, bands on the gel were visualised using G:Box (Syngene, Cambridge, UK) and Genesys software (Syngene, Cambridge, UK).

Protein separation and expression

Protein contents of lysed cells were separated using Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE); see Appendix A for components of resolving gel, stacking gel and electrode running buffer. A total protein concentration of 20µg was analysed, mixed with an equal volume of loading buffer (Laemmli sample buffer [2x] with dithiothreitol [DTT]) (Appendix A). Once separated by SDS-PAGE, differential protein expression in the variably treated MCF-7 cell samples was assessed using Western blotting. Separated proteins were transferred from fragile gel medium to a solid nitrocellulose membrane by soaking in transfer buffer (Appendix A) and running at 100V for 1 hour. The nitrocellulose membrane was then submerged in Ponceau S stain for 30 seconds and washed in 1x Tris-buffered saline (TBS)-Tween 20 (Appendix A) prior to incubation with primary antibody specific to the protein of interest, in this case the GR and a actin control (New England Biolabs Ltd, UK) (Appendix C). A 1:1000 rabbit primary antibody dilution made in 1% Marvel milk solution made up in 1x TBS-Tween 20 was used. The membrane was subsequently incubated with secondary antibody (1:5000 IgG horseradish peroxidase [HRP] conjugated anti-rabbit antibody), specific for the Fc region of the primary antibody, to allow protein visualisation upon chemiluminescent exposure. 100µl of chemiluminescent detection reagents (Appendix A) were applied to the nitrocellulose membrane. The G:Box (Syngene, Cambridge, UK) and GeneSys software were used to visualise protein bands.

Statistical Analysis

Where applicable, densitometry using ImageJ quantification software (U.S. National Institutes of Health) was used to analyse PCR and western blot bands. Statistically significant differences were assessed using the student's unpaired t-test and GraphPad software. Statistical significance was considered $p \leq 0.05$.

RESULTS

Fulvestrant treatment increases GR mRNA expression in MCF-7 cells. GR mRNA levels in MCF-7 breast cancer cell lines were compared by RT-PCR between cells given: no treatment (control/wild-type cells); 7-days of fulvestrant (100nM), or 7-days of oestrogen (1nM). Oestrogen-treated cells were included to provide the greatest differential for ER activity relative to fulvestrant. 7-day-fulvestrant-treatment visually up-regulated GR expression (Figure 1), though this was not statistically significant (Figure 2).

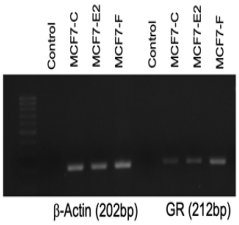

Figure 1: Example PCR run depicting GR mRNA (212bp) expression in MCF-7 breast cancer cell lines given: no treatment (MCF7-C), 7-day-oestrogen treatment (MCF7-E2) or 7-day-fulvestrant treatment (MCF7-F). A blank negative control (no cDNA, labelled 'control') is included to confirm lack of contamination. β-actin acts as a loading comparator.

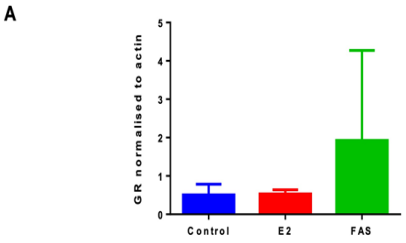

Figure 2: Densitometry analysis of GR mRNA expression in MCF-7 breast cancer cell lines. Density values were obtained in each cell line for control (no treatment), E2 (oestrogen treated, 1nM) and Fas (7-day-fulvestrant treated, 100nM) treated cells (n=3 for each). All comparisons versus control were non-statistically significant (p<0.05). Error bars depict standard deviation.

Increased GR mRNA expression is maintained in MCF-7 cells with acquired fulvestrant resistance.7-days of fulvestrant therapy is insufficient to evoke acquisition of a fulvestrant resistant phenotype, given clinically resistance does not manifest until 2-3 years after therapy initiation. (7) GR involvement in anti-hormone resistance thus demands increased GR mRNA be sustained in fulvestrant-resistant cells. GR mRNA expression was up-regulated in fulvestrant-resistant versus wild-type MCF-7 cells (Figure 3). Difficulties obtaining PCR bands in this resistant cell sample precluded densitometry (n=1).

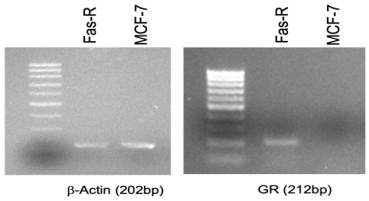

Figure 3: PCR analysis of GR mRNA expression in MCF-7 control/wild-type (no treatment) and fulvestrant-resistant (Fas-R) breast cancer cells. β-actin acts as a loading comparator.

GR protein expression is increased in fulvestrant and tamoxifen resistant MCF-7 cells .GR mRNA alterations must translate to the protein level to confer biological significance. Thus, GR protein expression in wild-type (control) MCF-7 cells was compared to 7-day-fulvestrant-treated (Fas), tamoxifen-resistant (Tam-R) and fulvestrant-resistant (Fas-R) cells. GR protein (94kDa) was expressed in all control and treated cells, and unequivocally increased in fulvestrant-resistant, tamoxifen-resistant and 7-day-fulvestrant-treated cells relative to control, though the increase was most pronounced in anti-hormone resistant cell samples, evidenced by markedly denser bands in both fulvestrant and tamoxifen resistance (Figure 4). The increase in GR protein in fulvestrant-resistant cells was statistically significant (p=0.0345) compared to control (Figure 5), supporting a potential role for the GR in anti-hormone resistance.

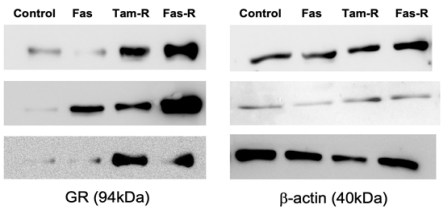

Figure 4: Western blots of GR protein expression in variably treated MCF-7 cells
Blots were probed using GR rabbit primary antibody. β-actin from the corresponding blots is included as a loading comparator and to check the efficiency of gel transfer. Blots shown are from 3 separate experiment Control=no treatment; Fas=7-day-fulvestrant-treated (100nM); Tam-R= tamoxifen resistant; Fas-R= fulvestrant resistant

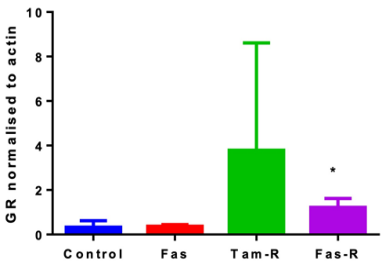

Figure 5: Densitometry analysis of GR protein expression in variably treated MCF-7 cells detected by western blot after normalisation to the corresponding β-actin. A statistically significant increase was seen between control versus fulvestrant-resistant cells (p=0.0345). Statistical significance was p<0.05(*). Error bars depict standard deviation (n=1). Control: no treatment; Fas: 7-day-fulvestrant-treatment; Tam-R: tamoxifen-resistant cells; Fas-R: fulvestrant-resistant cells

DISCUSSION

Since 1977, breast cancer has been the most prevalent cancer in females within the United Kingdom with approximately 75% of cases ER-positive. (26) The efficacy of anti-hormone agents such as fulvestrant is limited by development of resistance in a large cohort of patients. (4) Numerous underlying mechanisms have been postulated but, as of yet, fail to fully explain this acquisition of resistance. (27) Accordingly, this study investigated the potential role of the GR in driving resistant cell growth in the ER positive MCF-7 breast cancer cell line, with the aim of better understanding the resistance process.

At the mRNA level, alterations in GR expression in both 7-day-fulvestrant treated and fulvestrant-resistant cells were not statistically significant. Considering up-regulation was significant in resistance at the protein level, this may reflect the small sample size (n=3) of the study. Alternatively, particularly regarding 7-day-treated cells, it implies that transcriptional alterations require longer to manifest, and so do not become apparent until later on in the resistance process. This is not wholly unreasonable, given clinical indications of acquired resistance are only apparent 2-3 years after commencement of therapy. (4, 28)

In the present study, a meaningful contribution of the GR in endocrine resistance was suggested by observation of potent and statistically significant increase in GR protein up-regulation in fulvestrant-resistance. Tamoxifen-resistant cells also exhibited an increase in GR protein, though this was not statistically significant and could be reflective of the small sample size or a non-genuine change. In the ER positive MCF-7 cell line, other authors have observed reduced GR levels when compared to expression in ER negative cells, (29) which has subsequently been shown to result from oestrogen suppression of GR. (30-32) Therefore, the GR up-regulation observed in fulvestrant-resistant cells in this study may in part be explained by the essentially ER negative status, conferred by fulvestrant-mediated down-regulation of ER. (8) Interestingly, high GR expression in ER negative disease is also linked to worse disease free survival. (14) Hence, fulvestrant degradation of ER plausibly accounts for both the observed increase in GR with anti-hormone therapy and the negative clinical implications of this in terms of resistance.

Notably, the phenomenon of anti-hormone-induced GR up-regulation is not unique to breast cancer. Similar patterns have been observed in other, also predominately hormone-driven malignancies, such as prostate cancer, (33) with pharmacological androgen receptor (AR) blockade circumventing AR repression of GR levels, resulting in GR up-regulation. (34)

Dexamethasone, a GC, is routinely used alongside anti-hormones in breast cancer as a potent analgesic, or to relieve cancer-associated inflammatory symptoms. (20) Hence, implication of GR-mediated GC-induced transcription of survival genes in breast cancer has concerning implications surrounding the clinical worth of adjuvant GCs. (35, 36) Speculatively, if anti-hormone resistance is indeed stimulated by the GR, current practice of administering exogenous agonists such as dexamethasone, whilst beneficial in the short-term, could be having an overall detrimental impact. Hence, there is an urgent need for a prospective randomised controlled clinical trial investigating the effect of concomitant use of, and pre-treatment with, GCs.

The importance of ameliorating treatment-induced side effects cannot be downplayed. However, given the uncertainty of GCs in breast cancer, perhaps a different and safer approach should be employed, for example non-steroidal anti-inflammatory drugs. (37) Alternatively, concomitant use of anti-hormones with a GR antagonist, such as mifepristone, may show promise in delaying or preventing resistance, (38) though this needs further investigation. Furthermore, in experimental models of prostate cancer, the GR gene product SGK-1 was inhibited, resulting in reversal of resistance to androgen therapy. (34) Indeed, this may be superior to systemically administered GR inhibitors which would inevitably have widespread undesirable effects.

The overriding limitation of this study is the small number of experimental repeats performed which may mean observed changes have arisen due to random chance. Furthermore, breast cancer is clinically heterogeneous, with combinations of expressed receptors varying greatly and co-expression (or lack of) of notable significance. This study investigated only one cell line, MCF-7, which restricts the generalisability of conclusions drawn from the data. Future studies utilising other cell lines would thus be of value. Investigation of other hormonal therapies is also warranted, and particularly tamoxifen given its widespread use. Similarly, the widespread use of dexamethasone as an adjuvant therapy compels investigation into the biological changes this may be evoking.
In conclusion, the present study demonstrates significantly increased GR protein in both fulvestrant-resistant and tamoxifen-resistant MCF-7 cells, supporting the hypothesis that GR signalling may have a role in driving anti-hormone resistance in breast cancer. Given the implications of these data, and the scale of anti-hormone resistance in breast cancer, further confirmatory studies are necessitated.

REFERENCES

1. World Health Organisation. Early diagnosis and screening-Breast Cancer. Geneva: World Health Organisation; 2020 [accessed 8 Jun 2020]. Available from: https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en.

2. Howell A. Fulvestrant ('Faslodex'): current and future role in breast cancer management. Crit Rev Oncol Hematol. 2006;57:265-73.

https://doi.org/10.1016/j.critrevonc.2005.08.001

PMid:16473018

3. Williams C, Lin CY. Oestrogen receptors in breast cancer: basic mechanisms and clinical implications. Ecancermedicalscience. 2013;7:370.

4. Dixon JM. Endocrine resistance in breast cancer. New Journal of Science. 2014;2014:1-27.

https://doi.org/10.1155/2014/390618

5. Gee JM, Shaw VE, Hiscox SE, McClelland RA, Rushmere NK, Nicholson RI. Deciphering antihormone-induced compensatory mechanisms in breast cancer and their therapeutic implications. Endocr Relat Cancer. 2006;13 Suppl 1:S77-88.

https://doi.org/10.1677/erc.1.01274

PMid:17259561

6. Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer. 2009;9:631-43.

https://doi.org/10.1038/nrc2713

PMid:19701242

7. Rau KM, Kang HY, Cha TL, Miller SA, Hung MC. The mechanisms and managements of hormone-therapy resistance in breast and prostate cancers. Endocr Relat Cancer. 2005;12:511-32.

https://doi.org/10.1677/erc.1.01026

PMid:16172190

8. Hurvitz SA, Pietras RJ. Rational management of endocrine resistance in breast cancer: a comprehensive review of estrogen receptor biology, treatment options, and future directions. Cancer. 2008;113:2385-97.

https://doi.org/10.1002/cncr.23875

PMid:18819158

9. Jordan VC, O'Malley BW. Selective estrogen-receptor modulators and antihormonal resistance in breast cancer. J Clin Oncol. 2007;25:5815-24.

10. NICE. Fulvestrant for the treatment of locally advanced or metastatic breast cancer. London: NICE; 2011.

11. Salerno M, Sisci D, Mauro L, Guvakova MA, Ando S, Surmacz E. Insulin receptor substrate 1 is a target for the pure antiestrogen ICI 182,780 in breast cancer cells. Int J Cancer. 1999;81:299-304.

https://doi.org/10.1002/(SICI)1097-0215(19990412)81:2<299::AID-IJC21>3.0.CO;2-8

12. Osborne CK, Wakeling A, Nicholson RI. Fulvestrant: an oestrogen receptor antagonist with a novel mechanism of action. Br J Cancer. 2004;90 Suppl 1:S2-6.

https://doi.org/10.1038/sj.bjc.6601629

PMid:15094757 PMCid:PMC2750773

13. Clarke R, Tyson JJ, Dixon JM. Endocrine resistance in breast cancer - An overview and update. Mol Cell Endocrinol. 2015;418 Pt 3:220-34.

https://doi.org/10.1016/j.mce.2015.09.035 P

Mid:26455641 PMCid:PMC4684757

14. Garcia-Becerra R, Santos N, Diaz L, Camacho J. Mechanisms of resistance to endocrine therapy in breast cancer: focus on signaling pathways, miRNAs and genetically based resistance. Int J Mol Sci. 2012;14:108-45.

https://doi.org/10.3390/ijms14010108

PMid:23344024 PMCid:PMC3565254

15. Vu T, Claret FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. Front Oncol. 2012;2:62.

https://doi.org/10.3389/fonc.2012.00062

PMid:22720269 PMCid:PMC3376449

16. Isikbay M, Otto K, Kregel S, Kach J, Cai Y, Vander Griend D, et al. Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. Horm Cancer. 2014;5:72-89.

https://doi.org/10.1007/s12672-014-0173-2

PMid:24615402 PMCid:PMC4440041

17. Pan D, Kocherginsky M, Conzen SD. Activation of the glucocorticoid receptor is associated with poor prognosis in estrogen receptor-negative breast cancer. Cancer Res. 2011;71:6360-70.

https://doi.org/10.1158/0008-5472.CAN-11-0362

PMid:21868756 PMCid:PMC3514452

18. Chen Z, Lan X, Wu D, Sunkel B, Ye Z, Huang J, et al. Ligand-dependent genomic function of glucocorticoid receptor in triple-negative breast cancer. Nat Commun. 2015;6:8323.

https://doi.org/10.1038/ncomms9323

PMid:26374485 PMCid:PMC4573460

19. Buxant F, Kindt N, Laurent G, Noel JC, Saussez S. Antiproliferative effect of dexamethasone in the MCF-7 breast cancer cell line. Mol Med Rep. 2015;12:4051-4.

https://doi.org/10.3892/mmr.2015.3920

PMid:26080744 PMCid:PMC4526043

20. Wu W, Chaudhuri S, Brickley DR, Pang D, Karrison T, Conzen SD. Microarray analysis reveals glucocorticoid-regulated survival genes that are associated with inhibition of apoptosis in breast epithelial cells. Cancer Res. 2004;64:1757-64.

https://doi.org/10.1158/0008-5472.CAN-03-2546

PMid:14996737

21. Khan S, Lopez-Dee Z, Kumar R, Ling J. Activation of NFkB is a novel mechanism of pro-survival activity of glucocorticoids in breast cancer cells. Cancer Lett. 2013;337:90-5.

https://doi.org/10.1016/j.canlet.2013.05.020

PMid:23693080

22. Isikbay M, Otto K, Kregel S, Kach J, Cai Y, Vander Griend D, et al. Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. Horm Cancer. 2014;5:72-89.

https://doi.org/10.1007/s12672-014-0173-2

PMid:24615402 PMCid:PMC4440041

23. Moutsastsou P, Papavassiliou A. The glucocorticoid receptor signalling in breast cancer. J Cell Mol Med. 2008;12:145-63.

https://doi.org/10.1111/j.1582-4934.2007.00177.x

PMid:18053085 PMCid:PMC3823477

24. Vilasco M, Communal L, Mourra N, Courtin A, Forgez P, Gompel A. Glucocorticoid receptor and breast cancer. Breast Cancer Res Treat. 2011;130:1-10.

https://doi.org/10.1007/s10549-011-1689-6

PMid:21818591

25. Melhem A, Yamada SD, Fleming GF, Delgado B, Brickley DR, Wu W, et al. Administration of glucocorticoids to ovarian cancer patients is associated with expression of the anti-apoptotic genes SGK1 and MKP1/DUSP1 in ovarian tissues. Clin Cancer Res. 2009;15:3196-204.

https://doi.org/10.1158/1078-0432.CCR-08-2131

PMid:19383827 PMCid:PMC4707040

26. Cancer Research UK. Breast Cancer Statistics. London: Cancer Research UK; 2013 [accessed 18 March 2016]. Available from: http://www.cancerresearchuk.org.

27. Di Leo A, Curigliano G, Dieras V, Malorni L, Sotiriou C, Swanton C, et al. New approaches for improving outcomes in breast cancer in Europe. Breast. 2015;24:321-30.

https://doi.org/10.1016/j.breast.2015.03.001

PMid:25840656

28. Hayes EL, Lewis-Wambi JS. Mechanisms of endocrine resistance in breast cancer: an overview of the proposed roles of noncoding RNA. Breast Cancer Res. 2015;17:40.

https://doi.org/10.1186/s13058-015-0542-y

PMid:25849966 PMCid:PMC4362832

29. Hall RE, Lee CS, Alexander IE, Shine J, Clarke CL, Sutherland RL. Steroid hormone receptor gene expression in human breast cancer cells: inverse relationship between oestrogen and glucocorticoid receptor messenger RNA levels. Int J Cancer. 1990;46:1081-7.

https://doi.org/10.1002/ijc.2910460622

PMid:2249895

30. Krishnan AV, Swami S, Feldman D. Estradiol inhibits glucocorticoid receptor expression and induces glucocorticoid resistance in MCF-7 human breast cancer cells. J Steroid Biochem Mol Biol. 2001;77:29-37.

https://doi.org/10.1016/S0960-0760(01)00030-9

31. Rayburn ER, Ezell SJ, Zhang R. Anti-Inflammatory Agents for Cancer Therapy. Mol Cell Pharmacol. 2009;1:29-43.

https://doi.org/10.4255/mcpharmacol.09.05

PMid:20333321 PMCid:PMC2843097

32. Gong H, Jarzynka MJ, Cole TJ, Lee JH, Wada T, Zhang B, et al. Glucocorticoids antagonize estrogens by glucocorticoid receptor-mediated activation of estrogen sulfotransferase. Cancer Res. 2008;68:7386-93.

https://doi.org/10.1158/0008-5472.CAN-08-1545

PMid:18794126 PMCid:PMC6551207

33. Bhattacharyya RS, Krishnan AV, Swami S, Feldman D. Fulvestrant (ICI 182,780) down-regulates androgen receptor expression and diminishes androgenic responses in LNCaP human prostate cancer cells. Mol Cancer Ther. 2006;5:1539-49.

https://doi.org/10.1158/1535-7163.MCT-06-0065

PMid:16818513

34. Kach J, Conzen SD, Szmulewitz RZ. Targeting the glucocorticoid receptor in breast and prostate cancers. Sci Transl Med. 2015;7:305ps19.

https://doi.org/10.1126/scitranslmed.aac7531

35. Mitre-Aguilar IB, Cabrera-Quintero AJ, Zentella-Dehesa A. Genomic and non-genomic effects of glucocorticoids: implications for breast cancer. Int J Clin Exp Pathol. 2015;8:1-10.

36. Sui M, Chen F, Chen Z, Fan W. Glucocorticoids interfere with therapeutic efficacy of paclitaxel against human breast and ovarian xenograft tumors. Int J Cancer. 2006;119:712-7.

https://doi.org/10.1002/ijc.21743

PMid:16496381

37. Herr I, Gassler N, Friess H, Buchler MW. Regulation of differential pro- and anti-apoptotic signaling by glucocorticoids. Apoptosis. 2007;12:271-91.

https://doi.org/10.1007/s10495-006-0624-5

PMid:17191112

38. Skor MN, Wonder EL, Kocherginsky M, Goyal A, Hall BA, Cai Y, et al. Glucocorticoid receptor antagonism as a novel therapy for triple-negative breast cancer. Clin Cancer Res. 2013;19:6163-72.

https://doi.org/10.1158/1078-0432.CCR-12-3826

PMid:24016618 PMCid:PMC3860283

APPENDIX A

SOLUTIONS

Lysis Buffer (100mL), pH 7.6

> Tris base (50mM)	0.61g
> EGTA (5mM)	0.19g
> NaCl (150mM)	0.87g
> Triton (1%)	1ml

2X Laemmli Sample Buffer (10mL)

> 10% sodium dodecyl sulphate (SDS)	4ml
> 20% glycerol	2ml
> Tris buffer (0.5M, pH 6.8)	2.4ml
> Distilled water	1.6ml
> Bromophenol blue	1mg
> Dithiothreitol (DTT)	15.4mg

7.5% Acrylamide Resolving Gel (10mL)

> Distilled water	4.8ml
> Tris buffer (1.5M, pH 8.8)	2.5ml
> 30% Acyrlamide solution	2.5ml
> 10% Sodium dodecyl sulphate (SDS)	0.1ml
> 10% Ammonium persuplhate (APS)	0.1ml
> Tetramethylethylenediamine (TEMED)	6µl

4% Acrylamide Stacking Gel (10mL)

> Distilled water	6.1ml
> Tris buffer (2.5M, pH 6.8)	2.5ml
> 30% Acyrlamide solution	1.3ml
> 10% Sodium dodecyl sulphate (SDS)	0.1ml
> 10% Ammonium persuplhate (APS)	0.1ml
> Tetramethylethylenediamine (TEMED)	10µl

1X Running Buffer (1L)

> Tris base (0.25M)	3.02g
> Glycine (1.92M)	14.4g
> 0.1% sodium dodecyl sulphate (SDS)	1.0g

Transfer Buffer (1L)

> Tris Base (0.25M)	3.03g
> Glycine (1.92M)	14.4g
> 20% Methanol	200ml
> Distilled Water	800ml

1X TBS-Tween (1L)

> Tris base	1.21g
> NaCl	5.8g
> HCl (5M, pH 7.6)	1.5ml
> Tween 20	0.5ml

Ponceau S stain: 0.1% (w/v) in 5% acetic acid

5% Milk: 1.5g Marvel skimmed milk powder in 30mL 1X TBS-Tween

1% Milk: 0.5g Marvel skimmed milk powder in 50mL 1X TBS-Tween

Detection Reagents (Pierce and Warriner Ltd., Chester, UK)

> SuperSignal West Pico Chemiluminescent Substrate

> SuperSignal West Dura Chemiluminescent Substrate

> SuperSignal West Femto Chemiluminescent Substrate

APPENDIX B

PCR AND RT-PCR TECHNIQUES

Reverse transcription PCR Mastermix Solutions

> 5µl Deoxyribonucleotide Triphosphates (dNTP) (2.5mM)

> 4µl 5X PCR Buffer

> 2µl Random Hexamers (100µM)

Reverse Transcription Cycling Parameters

- 22°C, 10 minutes (annealing)
- 42°C, 42 minutes (chain elongation)
- 95°C, 5 minutes (denaturing)

PCR Mastermix Solution

- 18.75µl sterile RNA/DNAase free water
- 2.5µl 10X PCR buffer (Fisher Scientific, Loughborough, UK)
- 2µl deoxyribonucleotide triphosphates (dNTP) (2.5mM stock)
- 0.625µl of each primer (20µM stock)
- 0.75ul MgCl (50mM stock)
- 0.2µl Taq DNA Polymerase (Fisher Scientific, Loughborough, UK)

PCR Primer Sequences

B-actin

Forward: 5' GGA GCA ATG ATC TTG ATC TT

Reverse: 5' TCC TGA GGT ACG GGT CCT TCC

GR

Forward: 5' TCT GAA CTT CCC TGG TCG AA

Reverse: 5' GTG GTC CTG TTG TTG CTG TT

PCR Cycling Parameters

1st Cycle

- 95°C, 2 minutes (denaturation)
- 55°C, 1 minute (annealing)
- 72°C, 5 minutes (chain elongation)

Intermediate cycles

- 94°C, 30 seconds
- 55°C, 1 minute
- 72°C, 1 minute

Final Cycle

- 94°C, 1 minute
- 55°C, 1 minute
- 60°C, 10 minutes

2% PCR agarose gel (50ml)

> Agarose	2g
> 1X Tris acetate-EDTA buffer (TAE)	100ml
> RedSafe Nucleic Acid Staining Solution	5µL

DNA loading buffer

> 40% sucrose	4g
> Bromophenol blue (0.25%)	25mg
> Sterile pure nuclease free water	10ml

.

APPENDIX C

ANTIBODIES (NEW ENGLAND BIOLABS LTD, UK)

Primary Antibody Solutions (Dilution of 1 in 1000 in 1% milk)

Antibody	Animal origin species
GR	Rabbit
β-actin	Rabbit

Secondary Antibody Solutions (Dilution of 1 in 5000 in 1xTBS-TWEEN-20

Antibody	Primary Antibodies visualised
2° Anti-rabbit	GR

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Discussion article

‘When you hear hooves, think zebras’: further integrating the biopsychosocial model in medical education to help rare disease patients

DISCUSSION

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ABSTRACT

Diagnostic delay in individuals with a rare disease is, on average, 4.8 years. Their journey to diagnosis, often referred to as a diagnostic odyssey, is plagued by countless investigations and unsuccessful referrals. How can we ensure that healthcare professionals will consider rare diseases when first meeting a patient? The answer may lie in tackling the issue early on when clinicians begin their journey at medical school. The current medical school curriculum approach in the United Kingdom, which is largely based on the biomedical model, causes a hindrance in improving rare disease diagnosis. Bypassing the cultural, social and psychological considerations that a doctor has to address when treating a patient, may contribute to the diagnostic odyssey patients have to go through. Further integration of the biopsychosocial model into medical teaching can improve the diagnostic journey for patients as well as the patient-doctor relationship. The latter could lead to a shorter diagnostic delay by increasing compliance and engagement. Additionally, approaching a patient with the biopsychosocial model could help their wellbeing and mental health during their journey to diagnosis. Integrating rare disease teaching pre-clinically and clinically via student selected units (SSU), paediatrics and primary care placements, will equip future clinicians with an understanding of rare diseases to ultimately reduced diagnostic delay and improve the experience of those living with one.

Rare diseases - of which there are between 6,000 and 8,000 (1) - affect fewer than 5 in 10,000 people. (2) They are often overlooked in medical school education, clinical practice, and research funding. I was not aware of rare diseases until more than half-way through my medical degree, when I met AL (pseudonym). She had been on buprenorphine patches and codeine for osteoarthritis, but they had done little to relieve her pain. When I met her, my initial feeling was surprise; how could she have osteoarthritis in her late twenties? The culprit turned out to be Mucopolysaccharidosis type-I (MPS-I), a rare hereditary metabolic disorder. Individuals suffering from MPS-I lack the enzyme required for glycosaminoglycan degradation, leading to its accumulation in tissues, causing skeletal, neurological and cardiorespiratory problems. (3) AL suffers from osteopenia, osteoporosis, osteoarthritis, kyphosis, carpal tunnel syndrome and cardiovascular issues. These have all impaired her mobility and left her as a wheelchair user. Her limited vision and hearing impairment make it difficult for her to go out alone and have affected her mental health. As misfortune – or luck – would have it, AL suffers from a severe form of MPS-I; she started showing symptoms early on and her diagnosis was not overly delayed. This is imperative. Quick diagnosis in rare diseases has been associated with a significant reduction in morbidity and mortality. (4) Unfortunately, most people affected by rare diseases have a different diagnostic journey, often referred to as a diagnostic odyssey; (5) plagued by an array of misdiagnoses and futile investigations. Diagnostic delay is, on average, 4.8 years long. (6) Recommendations recently published to tackle time-to-diagnosis in rare diseases suggest that primary care healthcare professionals should be equipped with diagnostic tools and flow-chart pathways for rare disease identification. This would increase the likelihood that correct referrals are carried out. (5) Whilst this may accelerate time to diagnosis once a rare disease is considered, the clinician first has to regard it as a differential for the appropriate investigations and referrals to take place. How can we ensure that healthcare professionals will consider rare diseases when diagnosing a patient? The answer may lie in tackling the issue early on when clinicians begin their journey at medical school.

Currently, medical schools in the United Kingdom (UK) adopt one of following types of curricula: (1) traditional - a lecture-based curriculum where there is a clear pre-clinical and clinical divide; (2) problem-based learning where students learn by addressing an open-ended problem found in a trigger material; (7) or (3) a mixture of both. Regardless of the curriculum type, medical schools must comply with the General Medical Council (GMC) requirements, the UK public body in charge of the official register of doctors. (8) Generally speaking, the content of education across medical schools is biomedical in nature, although in varying degrees based on the institution and curriculum type used. This type of model is strictly focused on biological aspects of illness (9) and only superficially addresses the cultural, social and psychological considerations that a doctor has to address when treating a patient. The biomedical model reinforces the paternalistic idea that clinical decisions are made based on what the clinician deems to be in the patient's best interest. Within the model, patients' knowledge is considered poor when compared to the clinician, and it takes a secondary role when making treatment decisions. Perhaps it is these two aspects of the model, if instilled in medical students early on, that contribute to the diagnostic odyssey. This is for two main reasons.

Firstly, an individual who presents with a set of symptoms the clinician has never seen before poses a diagnostic challenge. Clinicians may not refer appropriately and investigations which might prove ineffectual may be performed. (3) Throughout this process, the patient's wellbeing and symptom control may suffer as frequent investigations take a toll on patients' mental health. These risks are typically not prioritised if a pure biomedical model is applied in clinical practice. Medical school education has, in the last decade, introduced elements of the biopsychosocial model in their teaching. This is a holistic and multifactorial approach to clinical practice which includes a strong focus on cultural, social and psychological issues. However, it is often integrated in the clinical years of placement and overshadowed by the practical skills medical students need to hone before becoming junior doctors. (7) Time and time again, medical students are reminded that "when you hear hooves, think horses not zebras." An aphorism coined in the late 1940s, (10) it serves as a reminder to medical students that common conditions are, by default, common. When a patient presents with certain symptoms or signs, you should always consider the most prevalent causes first before considering rarer differentials. Although important when teaching medical students how to approach a clinical consultation, by focusing too much on what is common, and often not considering what is rare, are we doing patients a disservice? I believe the diagnostic odyssey experience in patients with rare diseases would be improved if medical school programmes integrated the 'biopsychosocial' model earlier on by incorporating more behavioural and social sciences alongside pathophysiology and pharmacology. This is because by equipping students with "soft skills" developed through this model, future clinicians will be able to more promptly respond to the emotional needs of a patient who might still not have a diagnosis. Whilst this may not shorten their journey to diagnosis, it will hopefully improve their wellbeing and mental health whilst waiting for one.

A major challenge with achieving this is that the National Health Service (NHS) is a taxpayer-funded system that faces constant pressures due to under-staffing. Delivering holistic care in a system like this is not easy; most clinicians probably do recognise the emotional needs of their patients but responding adequately in a system dictated by short appointment times and ever-increasing workload is challenging. Crucially, it is because of these pressures that further integration of the 'biopsychosocial' model would better enable clinicians to respond to the needs of patients, especially those with rare disease or complex co-morbidities. Training individuals early on to weigh biomedical, social and psychological factors that affect a patient equally in every consultation means that they will have practised identifying which factors are most important to the patient and should be dealt with first. This is key, especially since appointments can be as short as eight minutes in duration. (11)
I wish I had witnessed this first-hand in the case of VL, a 7-year old child I met with Rasmussen Syndrome. It is a rare disease marked

by seizures that increase in frequency and severity due to brain inflammation. This then leads to hemiparesis which with time, continues to weaken and can lead to complete loss of limb function. (12) Conducting the consultation with VL's parents using a 'biopsychosocial' approach might have helped the clinician identify VL's parents' main concerns early in the conversation. It might have prompted the clinician to act on VL's parents' worry that as he grows up and becomes more active, his risk of injury, should he have a seizure or experience limb weakness, may increase. Indeed, a few weeks later he was injured as he was playing in a public playground, exactly as his parents had feared. This risk, which could have been initially mitigated with a referral for Occupational Therapy assessment, was not prioritised when using a biomedical approach as the social issues were not discussed during the consultation. Ultimately, this could have spared VL and his family the physical and psychological pain and engendered greater trust in the healthcare system.

While a biopsychosocial model might not always shorten time to diagnosis directly, it can indirectly shorten a patient's diagnostic odyssey by improving the relationship between the doctor and the patient. A 2019 observational study reported that consultations with conflicting points of views between the patient and the practitioner not only led to mistrust but to unhelpful patient behaviour (non-attendance). (13) This can lead to both patient harm and extended diagnostic delay; especially crucial in the context of rare diseases where symptoms and signs are often harder to diagnose and diagnostic delay is already unacceptably long. (6) Additionally, engagement between the clinician and the patient – which is a key component of the 'biopsychosocial' model – has been shown to improve diagnostic odyssey experience in rare diseases, (14) reinforcing the argument for its integration in the medical school curriculum earlier on.

Secondly, the inherent assumption perpetuated by the biomedical model that patients and family members' knowledge is poor, has to be removed early on. Over the months and years that patients live with a condition, they become experts on how to manage the symptoms they experience. Their expertise can aid diagnosis and reduce diagnostic delay but only if clinicians listen to their patients' concerns and expectations and accept that they may know less than their patient.

The biomedical model perpetuates this bias because it trains medical students to associate success with being able to identify and treat symptoms and signs of a disease, and not the individual as a whole. Treatment often focuses on something tangible that can be measured, like pharmacotherapy. This leads to an overshadowing of social and psychological aspects the patient might be concerned with. Better outcomes could be achieved if the patient's issues are being dealt with holistically and not only from a biomedical point of view. In the case of a rare disease like MPS-I, patients often struggle to use fine motor skills because of the pain they experience. If a piano teacher, still undiagnosed, was presenting to her general practitioner (GP) with arthritic-type symptoms, the clinician might focus on following a biomedical model to diagnosis and prescribe pharmacotherapy for the pain and refer for investigations. If you applied the biopsychosocial model you would also consider the threat to her job security. If she couldn't teach piano, how would she pay for her house and her bills? What effect would that have on her pain, her wellbeing and mental health? Could it indirectly negatively impact any other co-morbidities she may already have? Discussing this could lead to a referral to a link worker for social prescribing (15) which would then put the patient in contact with volunteer organisations and charities that can help with social issues. Applying the biopsychosocial model would not only focus on identifying the cause and treating the problem (the pain), which is an aspect of both the biomedical and biopsychosocial model, but on identifying interim solutions while the diagnosis is being pursued. This will make the investigations to diagnosis more manageable for the patient.

Adoption of a biopsychosocial approach has been extensively researched in chronic illness, autoimmune diseases, functional diseases and in psychiatry. (16-18) Its utilisation has been shown to improve patient trust and satisfaction, medication adherence once diagnosed, promote positive behavioural change and a better quality of life. (16-19) Research has also shown that the adoption of the biopsychosocial model can reduce the amount of diagnostic tests and referrals as the relationship fostered between the doctor and the patient reassures patients that a common ground can be found between both parties. (20) Rare diseases like MPS-I or Rasmussen syndrome are often chronic or progressive, which supports the argument for approaching patients who might have a rare disease using the biopsychosocial model.

Not only does the model lead to better health outcomes physically, but it can also address the non-biomedical aspects of living and the psychological factors that may affect patients' wellbeing. These, if given consideration, can be targeted with an appropriate intervention whilst developing an individual diagnostic and treatment strategy more specific to the array of symptoms and social issues the patient may face during diagnosis. (6) Additionally, patients with rare diseases often experience issues when communicating with medical professionals who do not believe their symptoms (21) or who are themselves frustrated with a lack of diagnosis. This has negative repercussions on both the patient and the length of time to diagnosis. (21) Theoretical knowledge of a disease is not a replacement for years of experience. Involving the patient in decision-making and in addressing what is important for the patient may not only shorten the diagnostic odyssey but may make the journey to diagnosis better and improve the rapport between patients and healthcare professionals.

Not only should the biopsychosocial model be integrated more fully in current medical curricula across the UK but changes should be made to the content of the curriculum itself. Until recently, there was no standardised curriculum across UK medical schools, the topics covered were partly dependent on what was deemed clinically useful, and partly on the healthcare opportunities available in the area. (22) With the introduction of the Medical Licencing

Assessment (MLA) curriculum (23) for the graduating year of 2023-24 this will change. The MLA curriculum outlines a list of conditions that medical students are required to understand by the time they graduate; this knowledge will then be tested in a national exam medical students will be required to sit in order to graduate. Encouragingly, a few rare diseases are mentioned in the MLA curriculum; muscular dystrophies, myeloproliferative disorders and polymyalgia rheumatica. However, two are umbrella terms for groups of conditions – muscular dystrophies, myeloproliferative disorders – and the curriculum does not specify how much time should be spent on each topic and in what format that should be taught. Understandably, as different curricula types employ different teaching methods, this gives medical schools the freedom to integrate the MLA curriculum requirements within their current curriculum without having to re-design a completely new course. However, as no timeframe is specified, this caveat might result in some universities deeming one lecture enough to fulfil the requirement while another could allocate a week of theoretical and clinical work to rare diseases. This would lead to a discrepancy in knowledge between graduating students from different institutions.

It is also important to consider that collectively, rare diseases affect 1 in 17 patients. (2) Tomorrow's doctors must be able to recognise a patient who could be affected by a rare disease, even if they cannot diagnose the rare disease at first presentation. Being able to consider a rare disease can only occur if students have engaged with patients who have experienced the diagnostic odyssey themselves - the signs and symptoms may be different in the patient they encounter as a clinician compared to the patient they met at medical school, but similar diagnostic patterns will be present. (24) Following GMC recommendation, this is already integrated to a varying extent in UK medical schools by having expert patients for conditions that medical students will often see as clinicians. So why not have some rare disease patients as expert patients? (25) After all, who better than someone who has lived through the diagnostic odyssey to explain to medical students their disease and experiences? It is not only beneficial for the patients that medical students will encounter in future, but to the students too, as engagement with expert patients has been reported to increase confidence in clinical decision making. (26) Self-confidence has been shown to be an important resource for effective clinical decisions that improve patient diagnosis and management. (27)

With over 180 rare disease patient organisations present in the UK, integrating rare diseases into medical school teaching via expert patients is a feasible short-term task. (28) It will provide future clinicians with an insight into rare diseases, the struggles of the diagnostic odyssey and an awareness into what living with a rare disease within the NHS is really like. Expert patient integration into the curriculum could then be followed by long-term curriculum changes, for example via student selected units and elective opportunities for students who wish to learn more about rare diseases. Additionally, medical schools could also integrate rare disease teaching in parts of the syllabus where they are commonly encountered, such as paediatrics and primary care. Future clinicians who choose to train in these specialties would therefore already have an understanding of rare diseases and how they may present before they qualify. All of these changes would, in turn, equip future clinicians with an awareness that is currently lacking in clinical practice and help rare disease patients by feeling heard, accounted for and considered. Ultimately, the patient's healthcare experience would be improved. Further integrating the biopsychosocial model and rare diseases teaching in medical education would enable current medical students to be better clinicians and to serve the purpose they set out to fulfil when they enrolled in medical school: care for people in need. People like AL.

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REFERENCES

1. Dawkins HJS, Draghia-Akli R, Lasko P, Lau LPL, Jonker AH et al. Progress in rare disease research 2010-2016: an IRDiRC Perspective. Clinical Translational Science. 2018;11(1):11-20.

https://doi.org/10.1111/cts.12501

PMCid: PMC5759730. PMid: 28796411

2. Rare Disease UK. What is a Rare Disease? London: Genetic Alliance UK; 2020 [accessed 9th Feb 2020]. Available at: https://www.raredisease.org.uk/what-is-a-rare-disease.

3. Soni-Jaiswal A, Mercer J, Jones SA, Bruce IA, Callery P. Mucopolysaccharidosis I: parental beliefs about the impact of disease on the quality of life of their children. Orphanet Journal of Rare Diseases. 2016;11:96.

https://doi.org/10.1186/s13023-016-0478-z.

PMCid: PMC4942895. PMid: 27406185

4. Polizzi A, Gentile AE, Taruscio D. Competing to raise awareness of rare diseases. Lancet Neurology. 2019;18(8):721-722.

http://doi.org/10.1016/S1474-4422(18)30437-X

PMid:30447970

5. Global Disease Commission. Ending the diagnostic odyssey for children with a rare disease. Zurich: Global Rare Disease Commission; 2018 [accessed 12th Feb 2020]. Available from: https://globalrarediseasecommission.com/Report.

6. Evans WRH. Dare to think rare: diagnostic delay and rare diseases. British Journal of General Practice. 2018; 68(670):224-225.

https://doi.org/10.3399/bjgp18X695957

PMid:29700025 PMCid:PMC5916061

7. Miles S, Kellett J, Leinster J. Medical graduate' preparedness to practice: a comparison of undergraduate medical school training. BMC Medical Education. 2017;17:33.

https://doi.org/10.1186/s12909-017-0859-6

PMid:28166769 PMCid:PMC5295184

8. General Medical Council. Promoting excellence: standards for medical education and training. London: GMC UK; 2016 [accessed 21st Jan 2020]. Available from: https://www.gmc-uk.org/-/media/documents/Promoting_excellence_standards_for_medical_education_and_training_0715.pdf_61939165.pdf.

9. Farre A, Rapley T. The new old (and old new) medical model: four decades navigating the biomedical and psychosocial understandings of health and illness. Healthcare. 2017;5(4):88.

https://doi.org/10.3390/healthcare5040088

PMid:29156540 PMCid:PMC5746722

10. Quote Investigator. When you hear hoofbeats look for horses not zebras. Quote Investigator; 2020 [accessed 15th Jan 2020]. Available at: https://quoteinvestigator.com/2017/11/26/zebras.

11. Oxyoby K. Consultation times. BMJ. 2010;340.

https://doi.org/10.1136/bmj.c2554

12. Orsini A, Costagliola G, Perna D, Esposito MG, Bonofilio L, Striano P et al. Efficacy and tolerability of mycophenolate mofetil in pediatric Rasmussen syndrome. Epilepsy Behav Rep. 2019;13:1000334.

http://doi.org/10.1016/j.ebr.2019.100334

PMid: 32140679 PMCid: PMC7044645

13. Amelung D, Whitaker KL, Lennard D, Ogden M, Sheringham ,. Zhou Y et al. Influence of doctor-patient conversations on behaviours of patients presenting to primary care with new or persistent symptoms: a video observation study. BMJ Quality and Safety. 2020;29:198-208.

http://dx.doi.org/10.1136/bmjqs-2019-009485

PMid:31326946 PMCid:PMC7057803

14. Budych K, Helms TM, Schultz C. How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient-physician interaction. Health Policy. 2012;105(2-3):154-64.

http://doi.org/10.1016/j.healthpol.2012.02.018

PMid:22464590

15. Moffatt S, Steer M, Lawson S, Penn L, O'Brien N. Link worker social prescribing to improve health and well-being for people with long-term conditions: qualitative study of service user perception. BMJ Open. 2017;7(7):e015203.

http://doi.org/10.1136/bmjopen-2016-015203

PMCid: PMC5541496 PMid: 28713072

16. Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW et al. The impact of patient-centered care on outcomes. Journal of Family Practice. 2000;49:796–804.

PMid:11032203

17. Drossman DA. Gastrointestinal illness and the biopsychosocial model. Journal of Clinical Gastroenterology. 1996;22:252–4.

https://doi.org/10.1097/00004836-199606000-00002

PMid: 8771417

18. Covic T, Adamson B, Spencer D, Howe G. A biopsychosocial model of pain and depression in rheumatoid arthritis: A 12-month longitudinal study. Rheumatology. 2003;42:1287–94.

http://doi.org/10.1093/rheumatology/keg369.

PMid:12810932

19. Williams GC, Frankel RM, Campbell TL, Deci EL. Research on relationship-centered care and healthcare outcomes from the Rochester biopsychosocial program: A self-determination theory integration. Journal of Families, Systems and Health. 2000;18:79–90.

http://doi.org/10.1111/j.1525-1497.2004.40901.x

PMCid: PMC1494796 PMid: 15566452

20. Ferrari R. The biopsychosocial model: a tool for rheumatologists. Best Practice and Research Clinical Rheumatology. 2000;14:787–95.

http://doi.org/10.1053/berh.2000.0113

PMid: 11092802

21. Rare Disease UK. The rare disease reality – an insight into the patient and family experience of rare disease. London: Genetic Alliance UK; 2016 [accessed 17th Jan 2020]. Available at: https://www.raredisease.org.uk/media/1588/the-rare-reality-an-insight-into-the-patient-and-family-experience-of-rare-disease.pdf.

22. Lee SWW, Clement N, Tang N, Atiomo W. The current provision of community-based teaching in UK medical schools: an online survey and systematic review. BMJ Open. 2014;4:e005696.

http://dx.doi.org/10.1136/bmjopen-2014-005696

PMid:25448625 PMCid:PMC4256542

23. General Medical Council. Medical Licencing Assessment. London: GMC UK; 2020 [accessed 21st Jan 2020]. Available from: https://www.gmc-uk.org/education/medical-licensing-assessment.

24. Blöß S, Klemann C, Rother A, Mehmecke S, Schumacher U et al. Diagnostic needs for rare diseases and shared pre-diagnostic phenomena: Results of a German-wide expert Delphi survey. PLoS One. 2017;12(2):30172532.

https://doi.org/10.1371/journal.pone.0172532

PMCid: PMC532530 PMid: 28234950

25. General Medical Council. Patient and public involvement in undergraduate medical education. London: GMC UK; 2020 [accessed 21st Jan 2020]. Available from: https://www.gmc-uk.org/-/media/documents/Patient_and_public_involvement_in_undergraduate_medical_education___guidance_0815.pdf_56438926.pdf.

26. Coulby C, Jha V. The role of patient-led education initiatives in medical education. Innovation and Entrepreneurship in Health. 2015;2:33-40.

27. Fry M, MacGregor C. Confidence and impact on clinical decision-making and behaviour in the emergency department. Australasian Emergency Nursing Journal. 2014;17(3):91-7.

http://doi.org/10.1016/j.aenj.2014.03.003

PMid:25113311

28. Genetic Alliance UK. Our Members. London: Genetic Alliance UK; 2020 [accessed 12th Jan 2020]. Available at: https://www.geneticalliance.org.uk/our-members.

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Education

Antimicrobial resistance: Where are we now?

EDUCATION

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ABSTRACT

Summary

This article discusses the global importance and multifactorial nature of the growing antimicrobial resistance (AMR) threat. It outlines how resistance arises at the level of the bacterium; including intrinsic and acquired resistance mechanisms. It also assesses current approaches to tackling AMR, both in the UK and worldwide, such as: drug development, calls for changes to medical, industrial and legislative practices, and antimicrobial-stewardship.

Relevance

With increasing numbers of multidrug resistant organisms causing infections worldwide, medical students must enter the workforce equipped with an understanding of the severity and origins of this situation as well as an appreciation of the steps being taken, and which they themselves can take as future clinicians, to address this challenge.

Take Home Messages

AMR is a multifactorial and continually evolving threat with its origins in the inherent genetic properties of microbes and their evolutionary nature. Consequentially, whilst urgent action is needed to combat an AMR problem exacerbated in recent decades, AMR will always persist. As microbes continually evolve new survival strategies, it is essential to continue to develop new pharmacological agents in conjunction with new practices and policies on institutional, national and international scales to protect global public health from the threat posed by AMR.

INTRODUCTION

Antibiotics were classically defined in 1947 by S. A. Waksman as natural substances that inhibit the growth of, or destroy, bacteria. In the current literature "antibiotic" may refer to any antimicrobial substance (toxic to viruses, fungi, protozoa or bacteria) that has natural, synthetic, or other origins. (1) Since the development of modern antibiotics in the early part of the 20th Century mortality from infectious diseases has declined significantly; illustrated by the 8.2% average annual decrease in infectious disease mortality in the USA from 1938 to 1952. (2) This was seen at the time as revolutionary, however contemporary optimism was to be undermined by the emergence of antimicrobial resistance (AMR). The current challenges and grave potential consequences posed by AMR to healthcare provision mean that it is essential for medical students, as future clinicians, to have an appreciation of the origins, causes and implications of AMR. In addition to addressing these issues, this article will discuss current strategies for tackling AMR both in the UK and around the world.

AMR describes the emergence of pathogen strains which have developed an immunity or resistance to antimicrobial drugs which previously had been lethal to that species. It is a consequence of evolution by natural selection and is exacerbated by the increased selection pressure applied to microbes by overuse of antibiotics. AMR is a rapidly developing problem which poses a significant threat to global health. (3)

AMR is not a new phenomenon. In his Nobel Prize lecture in 1945 Alexander Fleming himself warned of the risks of resistance stating that it was possible to produce resistant bacteria by exposing them to non-lethal concentrations of penicillin. (4) However, the scale and severity of the problem has grown in recent decades.

The bacteria identified as presenting the greatest AMR threat, and the causes of the majority of nosocomial infections worldwide, are collectively termed the "ESKAPE Pathogens" (summarised in Table 1). The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) have reported increases in the incidence of bacteraemia caused by each of the ESKAPE pathogens each year since 2014.(6) The global scale of the risk posed by these organisms, and others such as Mycobacterium tuberculosis, was summarised five years ago in a report by the World Health Organisation (WHO). (5) They reported that carbapenem-resistant Klebsiella pneumoniae is now present in all regions of the world, with carbapenem drugs ineffective in up to 50% of patients in some countries. They also report that in 2014 there were approximately 480 000 cases of multidrug-resistant Tuberculosis. 9.7% of these cases were Extensively Drug-Resistant Tuberculosis caused by M. tuberculosis which is resistant to four different antibiotics and found in 105 countries. In terms of global impact; the O'Neill Report estimates that by 2050, AMR related deaths will reach 10 million per year with an economic impact of up to $100 trillion. (3)

ESKAPE Pathogens				
Species Name	Gram Positive/Negative	Rate of bacteraemia per 100,000 population in England		
		2014	2018	Percentage Increase
Enterococcus faecium	Positive	-	-	
Staphylococcus aureus	Positive	19.4	23.2	19.59%
Klebsiella pneumoniae	Negative	9.1	12.1	32.97%
Acinetobacter spp.	Negative	1.3	1.5	15.38%
Pseudomonas spp.	Negative	6.4	7.6	18.75%
Enterobacter spp.	Negative	9.6	12.7	32.29%

Table 1:
ESKAPE Pathogens and the reported rate of bacteraemia attributed to these species according to the ESPAUR report 2018 to 2019 (6)

HOW DOES RESISTANCE ARISE?

Intrinsic Resistance

Some bacteria have intrinsic resistance to antibiotic drugs. This includes bacteria which lack the molecular targets of a specific antibiotic, and those with innate efflux mechanisms or cell walls which are highly impermeable. (7) Bacteria have varied and complex outer membranes composed of phospholipids and lipopolysaccharides meaning that they have varying susceptibility to cell wall acting antibiotics such as beta-lactams. Additionally, widely varied cell wall permeability found within gram-negative bacteria makes the discovery of effective antibiotics particularly challenging. (8)

Acquired Resistace

Unlike intrinsic resistance, acquired resistance mechanisms are not inherent properties of a given bacterial species – they are assimilated through random genetic mutation, from other bacteria or from the environment. (9)

Horizontal gene transfer (HGT) is one of the most prevalent strategies for conferring or acquiring AMR in bacteria. HGT involves the exchange of mobile genetic elements, containing 'resistance genes', between bacteria. Extra-chromosomal plasmids and conjugative transposons - which integrate into the genome of the recipient bacterium, can be transferred by conjugation or transformation. (10) AMR genes can also be acquired via bacteriophages through transduction, or through intra-genomic rearrangement, for example, involving insertion sequences. (11) Acquired AMR may also arise spontaneously through genetic mutation. For example, micro-organisms such as Helicobacter pylori have acquired resistance to Fluoroquinolones and Clarithromycin through mutation. (12, 13)

Acquired AMR mechanisms fall into three groupings:
• Prevention of the antibiotic accessing the target molecule within the bacterium
• Changes to this target molecule
• Direct modification or destruction of the antibiotic.

Bacteria may prevent antibiotics reaching their molecular targets by either decreasing permeability or by increasing efflux of the antibiotic. Decreased permeability may be achieved through the down regulation of transmembrane channels known as porins. Decreased porin expression has been shown to contribute to AMR in several species of Acinetobacter, Enterobacteraciaeae and Pseudomonas. (9) Increasing the efflux of an antibiotic can be achieved through the expression of efflux pumps. Efflux pumps are transmembrane structures which actively remove both endogenous and exogenous substances from the bacteria cytosol which are present across a wide variety of species. The use of these pumps to specifically remove antibiotics has been documented as a cause of AMR in many bacterial species including important human pathogens such as Legionella spp. and Brucella spp. (14)

Changes to the targets of antimicrobial agents by mutation, modification or protection of the target can all confer AMR. An example is resistance to Linezolid, an antibiotic which targets 23S ribosomal RNA subunits (rRNA). Most bacteria possess multiple copies of this gene and even single base-pair mutations have been shown to produce 23S rRNA which is impervious to Linezolid action, for example in Staphylococcus species. (15) Another way in which bacteria may protect their ribosomal components from antibiotic action is through methylation. The erm genes encode an enzyme which methylates both 23S and 50S rRNA subunits, impairing the ability of antibiotics such as macrolides to bind to these molecules. (16)

The third group of acquired AMR mechanisms is the direct modification or destruction of antibiotic drugs. The expression of enzymes for hydrolytic inactivation of antibiotics is a strategy employed by numerous bacterial species, for example, lactamase enzymes expressed by a variety of bacteria including Enterobacteriaceae. (17) Additionally, bacteria may modify antibiotics by adding chemical moieties such as nucleotides or phosphate groups to them thus reducing their ability to bind to their targets. Due to their chemical structure aminoglycoside antibiotics are particularly vulnerable to enzymatic modification by bacteria. (9)

ADDRESSING ANTIMICROBIAL RESISTANCE

One of the most prominent publications detailing strategies for combatting the rise in AMR is the O'Neill report commissioned by the UK Government in 2014 to investigate the threat posed by AMR and recommend international actions to address the problem. (3) The report's recommendations include strategies to reduce the need for antimicrobials by reducing infectious disease spread. Such strategies involve: increasing global public awareness, improving hygiene including access to clean water and sanitation and increased vaccination. Preventing infection will clearly reduce use of antimicrobials, reducing the rate of AMR development and preserving the utility of existing antimicrobial agents. (18) The UK is now is the middle of a five-year action plan (2019 to 2024) which builds upon This plan echoes many of the recommendations in the O'Neill report; its "three key ways" of tackling AMR are reduced antimicrobial exposure, optimised use and investment in innovation.

Antimicrobial Stewardship

In addition to reducing the overall need for antibiotics, the concept of antimicrobial-stewardship aims to optimise antibiotic prescribing through directing their use to only evidence based, appropriate indications. Some aspects of antimicrobial-stewardship have attracted controversy in recent years. Many studies have reported the benefits of these practices for slowing AMR development and improving patient outcomes. (20) However, some publications have suggested that actions such as delaying the start of antimicrobial treatment and early treatment de-escalation may have negative impacts on patient outcomes. Fitzpatrick et al. (21) discuss the "tension" between antimicrobial-stewardship and sepsis prevention. This may force clinicians and policy makers into difficult decisions between administering antibiotics for the potential benefit of the patient or withholding antibiotics for the potential benefit of the wider population. Furthermore, mathematical modelling by Obolski and colleagues suggests that restricting the use of antimicrobials may actually lead to increased emergence of multidrug resistant pathogens. (22). This may be due to, or exacerbated by, reduced antimicrobial prescribing leading to an increase in 'sub-lethal' exposure of bacterial populations to antibiotics and thus yielding more effective selection and exacerbating the AMR problem.

Rapid Diagnostics

Rapid diagnostics to reduce unnecessary antimicrobial use and target the use of narrow spectrum drugs, is a further proposal of the O'Neill Report, (3) and one which is already being appraised for use in clinical settings, with a range of positive and negative findings. Researchers have predicted the useful life of current last line antibiotics for Neisseria gonorrhoeae could be extended by point-of-care susceptibility testing – i.e. taking a patient sample, culturing the organism then testing its susceptibility to various antibiotics before deciding which one to prescribe , potentially postponing the situation where gonorrhoea becomes untreatable with current antibiotics. (23) On the other hand, in 2018 the National Institute for Health and Care Excellence (NICE) investigated point-of-care testing for Streptococcus A infection in patients presenting with sore throats. Their resultant briefing describes 11 tests, and states that there is "limited evidence" that such testing would change current antibiotic prescribing practices. (24) In November 2019 this research was incorporated into their Diagnostics Guidance in which they do not recommend this kind of rapid diagnostic testing for people aged over 5 years with sore throat symptoms. (25) The reasons are that Group A Streptococcus is not the only bacterial cause of sore throat symptoms, and that these symptoms are often self-limiting and thus rapid diagnostic testing of this nature does not represent pragmatic, cost-effective practice. Therefore, these NICE recommendations represent a more nuanced assessment of not just test accuracy and validity but also how testing fits into the broader clinical picture – a factor which is an important consideration for all novel testing practices.

Innovation and Development

Both the O'Neill Report and The UK Government's 5-year plan also advocate incentives for research and development of novel antimicrobials. (3,19) Suggestions include a Global AMR Innovation Fund of over $2 billion, market entry rewards and improved industry incentives. Such suggestions are designed to counteract a well-documented slump in the number of new antibiotics that have come to market in recent decades. Since the 1980's drug companies have increasingly shunned antimicrobial research in favour of more lucrative treatments for chronic and non-communicable diseases. (26) A further disincentive for novel antimicrobial research and design is reservation of novel drugs for second and third-line usage. Whilst this exemplifies good antimicrobial stewardship, it curtails the opportunity for pharmaceutical companies to generate profit and recoup development costs. For example, ceftaroline was added to the "Reserve Group" of antibiotics for "last resort" use in The WHO's List of Essential Medicines within 7 years of licencing by the Federal Drug Administration. (27,28) Many commentators have cited the lack of new antimicrobials as an exacerbating factor for the global AMR crisis. (29)

O'Neill's recommendations in this arena are supported by other publications calling for global changes to drug development, (3) licensing and funding policies in order to remove obstacles and incentivise large pharmaceutical companies to re-engage with antimicrobial research and development. (30) Legislative changes in the last decade give rise to hope that institutions and governments are taking note and enacting some of the demanded changes; however, there is limited evidence of the effectiveness of these measures and thus a need for greater international coordination. (31)

There are a multitude of ways to quantify and predict the future impact and costs of AMR including patient impact, impact on healthcare providers, the wider economic burden, and the perspective that any given study or prediction chooses to take can significantly alter their findings. (32) This variability is part of the reason that current health-economic models are unable to accurately incorporate the wider societal costs of increasing AMR.

Optimism can be drawn from several promising avenues of research into new drugs to treat resistant microbes. One such area is antibiotic adjuvants, also referred to as antibiotic resistance breakers (ARBs). ARBs are substances which increase or prolong the effectiveness of existing antimicrobial drugs by inhibiting bacterial resistance strategies. (33) lactamase enzyme inhibitors are among the oldest ARBs. Several decades of research have brought many candidate drugs into clinical trials although few have succeeded to clinical utility. Those which have made it to market include drugs which have improved the effectiveness of lactam antibiotics against resistant bacteria. (34)

In addition to preserving and improving existing drugs, novel classes of antibiotics are being discovered and investigated. Teixobactin is perhaps the most salient of the novel antibiotics currently in development. Teixobactin was discovered using an exciting new technology known as iChip, a device which can both capture traditionally unculturable environmental bacteria and collect the potential antibiotic compounds produced by these bacteria. (35) Teixobactin kills Gram-positive bacteria by binding to lipid molecules and inhibiting cell wall synthesis. Teixobactin and its analogues currently look promising in preclinical trials, for example proving to be effective treatments for methicillin-resistant S. aureus in murine models. (35) Additionally, review of the literature by Wright et al. found that cefiderocol, for example, is a promising novel antibiotic for the treatment of Gram-negative infections such as Pseudomonas aeurginosa. (36) However, these compounds have a long way to go through the clinical trials process before potentially reaching clinical utility.

It is also worth noting that almost all antibiotics are either natural microbial products or synthetic derivatives of microbial products. These phenotypic molecules, expressed in the context of evolution and natural selection, are complex and thus difficult to modify, replicate or synthesise on industrial scale. (37) Another implication is that these molecules exist due to an evolutionary race between microbes and thus antibiotic resistance long predates the clinical use of antimicrobial drugs. As a result, the potential for resistance to emerge to any novel compound exists long before that drug reaches clinical utility. (38)

CONCLUSION

Antimicrobial drugs have been one of the major medical achievements of recent centuries. However, the emergence of AMR and its increase in both prevalence and clinical significance in recent decades threatens to return us to an era of increased morbidity and mortality from infectious diseases. The mechanisms underpinning AMR are complicated, multifactorial and continually developing. Furthermore, the evolutionary nature of AMR means that resistance is likely to pose a challenge to all future antimicrobial drugs.

Increasing recognition among the medical and scientific communities matched by political will and increasing awareness and action by governments and global institutions, such as the WHO, have brought us action plans and strategies to combat the AMR crisis. Whether these plans can be implemented successfully and in an appropriately prompt manner remains to be seen.

REFERENCES

1. Mohr KI. History of Antibiotics Research. Curr Top Microbiol Immunol. 2016;398:237-272.

https://doi.org/10.1007/82_2016_499

PMid:27738915

2. Aminov, R. History of antimicrobial drug discovery: Major classes and health impact. Biochemical Pharmacology. 2017;133:4-19.

https://doi.org/10.1016/j.bcp.2016.10.001

PMid:27720719

3. O'Neill, J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London: The review on Antimicrobial Resistance; 2016 [accessed 9 Nov 2019]. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf.

4. Rosenblatt-Farrell, N. The Landscape of Antibiotic Resistance. Environmental Health Perspectives. 2009;117(6):A244-50.

https://doi.org/10.1289/ehp.117-a244

PMid:19590668 PMCid:PMC2702430

5. World Health Organisation. Antimicrobial resistance: Global report on surveillance. Geneva, Switzerland: World Health Organisaton; 2014.

6. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018 – 2019. London: Public Health England; 2019.

7. Cox G. and Wright G. Intrinsic antibiotic resistance: Mechanisms, origins, challenges and solutions. International Journal of Medical Microbiology. 2013;303(6-7):287-292.

https://doi.org/10.1016/j.ijmm.2013.02.009

PMid:23499305

8. Zgurskaya H, López C, and Gnanakaran S, Permeability Barrier of Gram-Negative Cell Envelopes and Approaches To Bypass It. ACS Infectious Diseases. 2015;1(11):512-522.

https://doi.org/10.1021/acsinfecdis.5b00097

PMid:26925460 PMCid: PMC4764994

9. Blair J, Webber M, Baylay A, Ogbolu D and Piddock L. Molecular mechanisms of antibiotic resistance. Nature Reviews Microbiology. 2014;13(1):42-51.

https://doi.org/10.1038/nrmicro3380

PMid:25435309

10. Von Wintersdorff C, Penders J, Van Niekerk J, Mills N, Majumder S, Van Alphen L, Savelkoul P and Wolffs, P. Dissemination of Antimicrobial Resistance in Microbial Ecosystems through Horizontal Gene Transfer. Frontiers in Microbiology. 2016;7.

https://doi.org/10.3389/fmicb.2016.00173

PMid:26925045 PMCid:PMC4759269

11. Van Hoek A, Mevius D, Guerra B, Mullany P, Roberts A and Aarts, H. Acquired Antibiotic Resistance Genes: An Overview. Frontiers in Microbiology. 2011;2:203.

https://doi.org/10.3389/fmicb.2011.00203

12. Jaka H, Rüttgerodt N, Bohne W, Mueller A, Gross U, Kasang C Mshana S. Helicobacter pylori Mutations Conferring Resistance to Fluoroquinolones and Clarithromycin among Dyspeptic Patients Attending a Tertiary Hospital, Tanzania. Canadian Journal of Gastroenterology and Hepatology. 2019;1-7.

https://doi.org/10.1155/2019/8481375

PMid:31355162 PMCid:PMC6634059

13. Wang G, Wilson T, Jiang Q and Taylor D. Spontaneous Mutations That Confer Antibiotic Resistance in Helicobacter pylori. Antimicrobial Agents and Chemotherapy, 2001;45(3):727-733.

https://doi.org/10.1128/AAC.45.3.727-733.2001

PMid:11181351 PMCid:PMC90364

14. Li X, Plésiat P. and Nikaido H. The Challenge of Efflux-Mediated Antibiotic Resistance in Gram-Negative Bacteria. Clinical Microbiology Review. 2015;28(2):337-418.

https://doi.org/10.1128/CMR.00117-14

PMid:25788514 PMCid:PMC4402952

15. Doern C, Park J, Gallegos M, Alspaugh D and Burnham C. Investigation of Linezolid Resistance in Staphylococci and Enterococci. Journal of Clinical Microbiology. 2016;54(5):1289-1294.

https://doi.org/10.1128/JCM.01929-15

PMid:26935728 PMCid:PMC4844726

16. Munita J and Arias C. Mechanisms of Antibiotic Resistance. Microbiology Spectrum, 2016;4(2).

https://doi.org/10.1128/microbiolspec.VMBF-0016-2015

PMid:27227291 PMCid:PMC4888801

17. Shaikh S, Fatima J, Shakil S, Rizvi S and Kamal M. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi Journal of Biological Sciences. 2015;22(1):90-101.

https://doi.org/10.1016/j.sjbs.2014.08.002

PMid:25561890 PMCid:PMC4281622

18. Dyar O, Huttner B, Schouten J and Pulcini C. What is antimicrobial stewardship? Clinical Microbiology and Infection. 2017;23(11):793-798.

https://doi.org/10.1016/j.cmi.2017.08.026

PMid:28882725

19. Department of Health and Social Care. UK 5-year action plan for antimicrobial resistance 2019 to 2024. London: Department of Health and Social Care; 2019.

20. Schuts E, Hulscher M, Mouton J, Verduin C, Stuart J, Overdiek H, van der Linden P, Natsch S, Hertogh C, Wolfs T, Schouten J, Kullberg B and Prins J. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. The Lancet Infectious Diseases 2016;16(7):847-856.

https://doi.org/10.1016/S1473-3099(16)00065-7

21. Fitzpatrick F, Tarrant C, Hamilton V, Kiernan F, Jenkins D and Krockow E. Sepsis and antimicrobial stewardship: two sides of the same coin. BMJ Quality & Safety. 2019;28(9):758-761.

https://doi.org/10.1136/bmjqs-2019-009445

PMid:31018985 PMCid:PMC6860726

22. Obolski U, Stein G and Hadany L. Antibiotic Restriction Might Facilitate the Emergence of Multi-drug Resistance. PLOS Computational Biology. 2015;11(6):1004340.

https://doi.org/10.1371/journal.pcbi.1004340

PMid:26110266 PMCid:PMC4481510

23. Turner K, Christensen H, Adams E, McAdams D, Fifer H, McDonnell A and Woodford N. Analysis of the potential for point-of-care test to enable individualised treatment of infections caused by antimicrobial-resistant and susceptible strains of Neisseria gonorrhoeae: a modelling study. BMJ Open. 2017;7(6):015447.

https://doi.org/10.1136/bmjopen-2016-015447

PMid:28615273 PMCid:PMC5734280

24. National Institute for Health and Care Excellence. Point-of-care diagnostic testing in primary care for strep A infection in sore throat. Medtech innovation briefing. London: NICE; 2018 [accessed 10 Nov. 2019]. Available at: https://www.nice.org.uk/advice/mib145/resources/pointofcare-diagnostic-testing-in-primary-care-for-strep-a-infection-in-sore-throat-pdf-2285963457844165.

25. National Institute for Health and Care Excellence. Recommendations- Rapid tests for group A streptococcal infections in people with a sore throat - Guidance. London: NICE; 2019 [accessed 11 Jan. 2020]. Available at: https://www.nice.org.uk/guidance/dg38/chapter/1-Recommendations.

26. Darrow J and Kesselheim A. Drug Development and FDA Approval, 1938–2013. New England Journal of Medicine. 2014;370(26):39.

https://doi.org/10.1056/NEJMp1402114

PMid:24963591

28. Mpenge M and MacGowan A. Ceftaroline in the management of complicated skin and soft tissue infections and community acquired pneumonia. Therapeutics and Clinical Risk Management. 2015;11:565.

https://doi.org/10.2147/TCRM.S75412

PMid:25897241 PMCid:PMC4396454

29. Ventola, C. The antibiotic resistance crisis: part 1: causes and threats. Pharmacy & Therapeutics. 2015;40(4):277-83.

30. Bax R and Green S. Antibiotics: the changing regulatory and pharmaceutical industry paradigm. Journal of Antimicrobial Chemotherapy. 2015;70(5):1281-1284.

https://doi.org/10.1093/jac/dku572

PMid:25634991

31. Simpkin V, Renwick M, Kelly R and Mossialos E. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. The Journal of Antibiotics. 2017;70(12):1087-1096.

https://doi.org/10.1038/ja.2017.124

PMid:29089600 PMCid:PMC5746591

32. Naylor N, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, Knight G and Robotham J. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrobial Resistance & Infection Control. 2018;7(1).

https://doi.org/10.1186/s13756-018-0336-y

PMid:29713465 PMCid:PMC5918775

33. Laws M, Shaaban A and Rahman K. Antibiotic resistance breakers: current approaches and future directions. FEMS Microbiology Reviews. 2019;43(5):490-516.

https://doi.org/10.1093/femsre/fuz014

PMid:31150547 PMCid:PMC6736374

34. Drawz S and Bonomo R. Three Decades of Lactamase Inhibitors. Clinical Microbiology Reviews. 2010;23(1):160-201.

https://doi.org/10.1128/CMR.00037-09

PMid:20065329 PMCid:PMC2806661

35. Piddock L. Teixobactin, the first of a new class of antibiotics discovered by iChip technology?. Journal of Antimicrobial Chemotherapy. 2015;70(10):2679-2680.

https://doi.org/10.1093/jac/dkv175

PMid:26089440

36. Wright H, Bonomo R and Paterson D. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn?. Clinical Microbiology and Infection. 2017;23(10):704-712.

https://doi.org/10.1016/j.cmi.2017.09.001

PMid:28893690

37. Fischbach M. Antibiotics from microbes: converging to kill. Current Opinion in Microbiology. 2009;12(5):520-527.

https://doi.org/10.1016/j.mib.2009.07.002

PMid:19695947 PMCid:PMC3176294

38. Wright G and Poinar H. Antibiotic resistance is ancient: implications for drug discovery. Trends in Microbiology. 2012;20(4):157-159.

https://doi.org/10.1016/j.tim.2012.01.002

PMid:22284896

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Education

Getting informed on informed consent: a guide for medical students

EDUCATION

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ABSTRACT

Summary

This paper provides guidance on the law surrounding informed consent, pitched at a medical school level. It will differentiate basic consent from informed consent, examine the surrounding case law (in particular Montgomery v Lanarkshire Health Board [2015]), providing the facts of key cases and the significant consequences of the judgements in order to ground abstract legal principles in practical examples. It makes suggestions on how to tailor practice to ensure that an informed consent is obtained.

Relevance

It is apparent that an understanding of law surrounding clinical practice is highly applicable to medical students and is often a dedicated learning outcome on the syllabus. 'Consenting a patient' is a process that takes place many times every single day and is a prominent part of any doctor's career, from every time they take blood to perform major surgery. It is vital that students understand the laws surrounding this process and what is required of them both now and in the future.

Take Home Messages

The case of Montgomery legally enforces a process of enabling autonomous decision making by the patient rather than paternalistically determining the direction of management. Informed consent requires that material and relevant risks be disclosed to the patient for both the recommended and alternative treatment plans. To achieve this, and determine what is material for that patient, obtaining informed consent requires a dialogue between doctor and patient.

INTRODUCTION

Consent is a concept that underpins every intervention a doctor will undertake for a patient. This ranges from insertion of a cannula to amputation of a limb. Not obtaining an informed consent can have dire consequences for both doctors and patients. It is not something that is to be taken for granted, yet many do not appreciate the complexities of both the legal and practical requirements. Even before qualification, students are bound by the laws on consent in much the same way doctors are. It is therefore pertinent to understand what these laws ask of us, and how they have come about. This paper sets out to provide a comprehensive coverage of the law surrounding informed consent and make suggestions as to what can be done to obtain it, whilst providing the context of the legal cases so as to minimise the abstract nature of the legal principles.

The Legal Roots of Real Consent and Informed Consent

The first step to ensuring consent is acknowledging that a patient must have capacity. An adult with capacity has an absolute right to determine what interventions they will undergo. Capacity is presumed to be present unless proven otherwise. The test held in the Mental Capacity Act 2005 is better described as a test for the 'lack of capacity'. Section 3 of the Act holds that a person is unable to make a decision for themselves if they cannot firstly understand the information relevant to the decision, secondly retain that information, thirdly weigh up that information, and finally communicate their decision having considered that information. This test is time and decision-specific, rather than patient-specific, meaning that the assessment is of the patient's ability to make a specific decision at the time it needs to be made. Patients should be supported to make these decisions through provision of practical help and advocates or translators if necessary. Those adults lacking capacity should be provided with best interests care as under the Mental Capacity Act 2005.

Once capacity is determined, one may consider obtaining consent from their patient to carry out an intervention. In essence, a real consent gives a doctor legal permission to physically act on a patient without being charged with battery. Battery is the "unlawful application of force by the defendant [here, the doctor] upon the victim [here, the patient]". (1) The word force is defined as "any intentional touching of another person without the consent of that person and without lawful excuse."(2) It therefore does not need to be aggressive or hostile in nature. To obtain a 'real consent', the patient must be informed about what the procedure involves and freely give permission for the doctor to act. (3)

This is a significantly lower standard than what is expected in informed consent. Informed consent is required for the doctor to avoid liability under the laws of negligence as opposed to battery. Broadly, a doctor is negligent if they fail to exercise appropriate care to an expected standard. The root of informed consent is based more on the ethical duty to facilitate the autonomy of the patient's decision making, rather than the legal permission to physically touch a patient. Thus, combining these two principles, a doctor would be negligent in obtaining informed consent if they failed to utilise the required care in ensuring a patient was able to exercise their autonomous decision making most effectively. The patient can make decisions considered unwise by the medical professional, and if the intervention is undergone in the absence of consent, it will be criminal assault. As put by Judge Peter Jackson "the fact that the intervention is well-meaning or therapeutic makes no difference". (4)

The right to consent also protects patients where they may have been deceived as to the nature of the intervention. This has been demonstrated by Potts v North West Regional Health Authority [1983] a patient was given a long acting contraceptive despite having been consented to a "routine post-natal vaccination". (5) Consent to an act, such as a breast exam in R v Tabassum [2000], is also negated if the reasoning given for it to take place is dishonest; in this case a breast examination was motivated by sexual purpose rather than medical examination. (6)

Case Law Development of Informed Consent

The contemporary answer as to what corresponds an 'informed' consent begins with the case of Montgomery. Montgomery was a particularly small woman with diabetes. She gave birth to a child in October 1999. The doctors caring for her during her pregnancy and labour had not informed her of an approximate 10% risk of shoulder dystocia (where the shoulder of the baby becomes stuck behind the pubic symphysis during birth). On this basis, a vaginal birth as opposed to a caesarean section was attempted. The son was then born with cerebral palsy, a recognised complication of shoulder dystocia. It was argued that, since the risk of cerebral palsy was not disclosed to Montgomery, she had not been enabled to make an autonomous decision considering all the relevant facts, and so had not given informed consent to her management.

Initially, the argument of Montgomery was dismissed. At that point, a 1985 law required doctors to disclose information that a 'responsible body of medical opinion thought appropriate'. (7) This was a paternalistic approach which allowed the doctor to control the amount of information given to patients and thus, potentially, ultimately determine a patient's management for them rather than with them.

However, following appeals to the Supreme Court in 2015, this position was changed, and the 'Montgomery approach' was adopted. (8) The core requirement of this is that in order to attain an informed consent, doctors must take reasonable care to ensure patients are aware of the material risks and benefits of a recom-

mended management plan and thus, the interventions required, as well as those of reasonable alternative courses of actions. Legally, the courts will ask two questions to determine if an 'informed consent' is reached. Firstly, given the circumstances of this patient, would a reasonable person in that position attach significance to the given risk? Secondly, should the doctor have reasonably been aware that the patient would attach significance to it? (8)

Other cases provide further guidelines to form a complete definition of informed consent.

In the case of A v East Kent Hospitals [2015], it was held that the chance of Mrs A's child being born with chromosomal abnormalities was 1 out of 1000, this was determined to be "theoretical, negligible, or background" and thus immaterial. It was also considered whether the claimant would have further investigated or terminated the pregnancy had the abnormality been found. (9) However, it is insufficient to rely purely on the numerical chances of something occurring.

Whether a risk is significant or not is determined by factors such as the severity of its consequence, the potential impact it would have on that patient, the nature of the harm, and the potential benefits. This was reflected in the case of Spencer v Hillingdon Hospital NHS Trust [2015] where following an operation on inguinal hernias, a patient developed bilateral pulmonary emboli. Although the risk of this was much smaller, 1 in 50 000, given the potential severity of the outcome it was a material risk. (10) The potential severity of a risk to that individual is also a key determinant in what is material. A 1 in 1000 risk of damage to the hand could be much more relevant to a patient who was a concert pianist than an average member of the public.

In cases where patients rely on incorrect knowledge, a doctor will be liable if they either hold responsibility for this misunderstanding, or, they should have realised the misunderstanding has occurred but took no steps to rectify it. (11) This was shown in the case of Worrall v Antoniadou [2016]. In this case, the claimant had breast augmentation surgery for her wedding. She was then advised a secondary procedure (a mastopexy) would be required within 10 months of the surgery. The claimant believed she would not require a procedure for 5 to 10 years, whereas the defendant had stated she would need another procedure 'sooner or later'. The case hinged therefore on whether the defendant was firstly responsible for the incorrect belief, and whether the defendant had taken sufficient steps to dispel the claimant's incorrect belief.

The rationale behind this can help to clarify what Montgomery is trying to achieve. Initially it involves recognising the importance of patient-centred care and treating each person as a distinct individual. Secondly, it recognises clinical decision making is not to be taking place behind closed doors. The General Medical Council wish for doctors and patients to engage in determining treatment options. The patient is the autonomous individual to decide which treatment path is best suited to their life, and what for them would be the optimal outcome. However, the patient is reliant on the doctor to shed light on those paths. Thus, there is a reciprocal relationship required. Since it is of no benefit to bombard a patient with every single possible risk and overload them, it is required for the doctor to exercise discretion as to which potential risks and benefits are most important for that patient's goals. The doctor is there to facilitate the patient's decision making. Only by providing that information is the patient able to make an educated decision on the path they wish to pursue, and thus, provide consent for what is going to happen to them. (12, 13)

Practicalities of Obtaining Informed Consent

The key takeaway from Montgomery is that to obtain informed consent, one must enter a 'dialogue' with the patient. It is helpful to set certain goals to have been reached by the end of this dialogue for both the patient and the doctor. The patient should understand the extent and severity of their condition. They should understand the expected benefits and inherent risks of the proposed method of management. They should be aware of other management options, how they differ and compare to the recommended one.

On the other hand, the doctor should feel the patient is sufficiently informed of the above to make a personalised decision. They should appreciate what the patient would consider a good outcome. They should understand what risks are important to that patient. They should have taken the opportunity to apply these factors to their recommended management plan. They should understand why a patient has come to a particular decision.

The content of this dialogue is not purely limited to medical factors. (14) It includes the particular values, needs, interests, and circumstances of that patient in a medical and social context. The doctor should understand how the patient hopes to see their quality of life being improved with a holistic approach rather than a simply biological one. This is because the concept of 'risk' is relative. An acceptable or unacceptable risk varies from person to person; and a doctor must not subjugate their perspective onto that of their patient.

The doctor should determine how much information a patient wishes to receive, and how they wish to receive it. (15) The information should then be conveyed in a manner which is appropriate for that patient. As expressed in Montgomery "routinely demanding [her] signature on a consent form" is insufficient. The adequacy of communication is more important than the method. This may take the form of leaflets, hand-drawn diagrams of physiology and interventions, or through signposting to useful educational resources. (16) Sufficient de-jargoning should have taken place. Given how little information may be retained in a singular consultation, it may be useful to write down the key concepts for the patient to come back to. The burden of explanation is explicitly placed on the medical professional to be forthcoming with the required information, rather than expecting the patient to ask the correct questions. (17) Patients should be encouraged and enabled to ask the doctor questions and clarify issues. An opportunity to do so should be provided at regular intervals. Comprehension should be ensured at the end of the consenting process; for example, this could be through asking the patient to explain back to you what you have told them. Finally, the patient should have been provided adequate time and space to process and determine their wishes before the procedure takes place. In practice, this suggests it would be bad practice to consent someone in the anaesthetics room before an operation since they could feel rushed or pressured to accept the proposed operation rather than consider the alternatives thoroughly. In line with the Royal College of Surgeons of England, better practice would involve consenting a patient in clinic. This allows time to discuss the surgery and the patient can reflect on the discussion. Confirming consent on the day of the procedure ensures that nothing has changed in that period. (18)

The importance of surgery consent can be illustrated by the case of Thefaut v Johnson [2017]. In this case, Mrs Thefaut underwent an elective discectomy, unfortunately resulting in nerve damage, pain, and a loss of function in her lower half. The consenting process for this case took place via a 5-minute telephone consultation, a follow-up letter, and a conversation immediately prior to the surgery. There were also concerns that the letter overestimated the benefits and underestimated the risks. It was held that this did not demonstrate the required 'time and space' for a reasonable dialogue to meet the Montgomery informed consent threshold. (19)

CONCLUSION

A real consent protects a medical professional from liability from battery. However, the standard of informed consent to avoid negligence is significantly higher. Informed consent requires doctors to make sure that patients are aware of material risks. It places an emphasis on the nature of that patient and what benefits and risks are of most significance to them. To obtain informed consent, one must enter into a dialogue with the patient. This is to facilitate a joint decision-making process which steps away from previous paternalistic approaches. The process of consenting a patient should be done in good time, in a manner which suits that patient, and enables a good working relationship where patients are empowered to ask questions and determine their own futures.

REFERENCES

1. R v Ireland [1997] 3 WLR 534

2. Faulkner v Talbot [1981] 3 All ER 468

3. Chatterton v Gerson [1981] QB 432, 443

4. Heart of England NHS Trust v JB [2014] EWHC 342

5. Potts v North West Regional Health Authority, The Guardian 23 July 1983

6. R v Tabassum [2000] Lloyd's Rep Med 404

7. Sidaway v Bethlem Royal Hospital [1985] AC 871 applying Bolam v Friern Hospital Management Committee [1957] 1 WLR 582

8. Montgomery v Lanarkshire Health Board [2015] UKSC 11

9. A v East Kent Hospitals [2015] UWHC 1038

10. Spencer –v- Hillingdon Hospital NHS Trust [2015] EWHC 1058

11. Worrall v Antoniadou [2016] EWCA Civ 1219

12. General Medical Council. Consent: patients and doctors making decisions together. London: GMC UK; 2008 [accessed 19 July 2020]. Available from: http://www.gmc-uk.org/guidance/ethical_guidance/consent_guidance_index.

13. Herring J, Fulford K, Dunn M, Handa A. Elbow Room for Best Practice? Montgomery, Patients' Values and Balanced Decision Making in Person-Centred Clinical Care. Medical Law Review. 2017;25(4):582-603.

https://doi.org/10.1093/medlaw/fwx029

PMid:28985348

14. Aintree University Hospitals v James [2013] UKSC 67

15. Webster v Burton Hospitals NHS Foundation Trust [2017] EWCA Civ 62

16. Al Hamwi v Johnson and another [2005] EWHC 206

17. Rodney Crossman v St George's Healthcare Trust [2016] EWHC 2878 (QB)

18. Royal College of Surgeons of England, 3.5.1 Consent. London: RCoS; 2014 [accessed 19 July 2020]. Available from: https://www.rcseng.ac.uk/standards-and-research/gsp/domain-3/3-5-1-consent.

19. Thefaut v Johnston [2017] EWHC 497 (QB) (14 March 2017)

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Education

An overview of the epidemiology, transmission, pathogenesis and treatment of scabies

EDUCATION

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ABSTRACT

Summary

Scabies is a well-known, yet a poorly understood neglected tropical disease (NTD). Although less common in the UK, scabies epidemics regularly occur abroad, in tropical, less developed communities (LDCs). Cases are prevalent in communities which tend to live with overcrowding, poor sanitation and limited access to healthcare facilities and medication. This environment provides the perfect breeding ground for the growth and the transmission of scabies. The body has a delayed response to infestation - this is due to the scabies mites' ability to disrupt the complement cascade and delay the onset of the adaptive arm of the immune response.

Relevance

Contrary to popular belief, anyone can become infested with scabies. Although not usually life-threatening, scabies can cause unpleasant symptoms as well as worsen existing skin conditions, which can reduce a person's quality of life. Prompt diagnosis is challenging in LDCs. Undiagnosed scabies may lead to serious complications such as secondary skin sepsis as well as allowing further transmission. Scabies is highly contagious; clinicians should be aware how to spot and treat scabies early on, and additionally know to offer treatment to other individuals that the patient has been in close contact with.

Take Home Messages

Management for scabies is relatively simple and involves the application of topical medication, such as Permethrin. Despite this, there are still many barriers to treating epidemics in LDCs, such as a lack of access to treatment and healthcare professionals, a lack of awareness from clinicians about the condition's clinical manifestations, as well as lack of infrastructure to definitively diagnose the condition. Despite progress in management of the condition, the pathophysiology and transmission of the condition are only partly understood, and the rise of resistance to current scabicides is indicative of the need for newer treatments, especially within resource-poor communities.

INTRODUCTION

The World Health Organisation (WHO) defines neglected tropical diseases (NTD) as 'a diverse group of communicable diseases that prevail in tropical and subtropical conditions in 149 countries.' (1) It is currently estimated that NTDs affect over 1 billion people, the majority of which live in less developed communities (LDCs), which have a lack of sanitation and healthcare access. This lack of access facilitates the spread of communicable diseases, potentially leading to preventable complications, such as blindness, physical deformities, and neurological problems. (2) The grouping of NTDs has led to their increased awareness amongst clinicians and has provided a compelling platform to derive specific management plans. Recent evidence has suggested that investments addressing NTDs is cost-effective for developing economies. More people cured will ensure a larger, healthier work force, consequently boosting the economy of developing nations. (3)

There are currently 17 NTDs including the well-known skin disease scabies. Skin diseases are one of the most frequent reasons for GP consultation. Skin diseases represented 8.4% of German consultations in 2010, with this set to increase globally. (4) Most patients with dermatological problems are only treated by their GP and are not referred further. (5) Although the prevalence of scabies in the UK is low, the condition still has global importance. Therefore, all clinicians should be aware of scabies, as well as understand how to diagnose and treat it, due to its profound impact on the skin. Skin protects internal organs, thermoregulates, allows sensation, forms vitamin D and therefore regulates calcium and phosphate levels in the body, acts as a physical barrier to the entry of foreign substances/ pathogens and is aesthetically important. (6)

Scabies is defined in two major forms, ordinary scabies (OS) and the more severe, crusted scabies (CS). (7) Both manifest from the same species of mite, thus management and treatment are largely the same between the conditions. This piece aims to discuss the epidemiology, transmission, clinical manifestation, and the pathophysiology of scabies, as well as the body's subsequent immunological response to the disease. In addition, this piece will describe the use of mass drug administration (MDA) as a treatment in LDCs with a scabies endemic, before briefly outlining the future of the methods of diagnosis and management of scabies.

Epidemiology

Scabies predominantly affects children and the elderly in the developing world, regardless of gender or race. Regions with the highest prevalence of scabies include India, the South Pacific and Northern Australia (which includes the Aboriginal community, which has the highest prevalence for CS). Communities based in these densely populated, tropical areas tend to live with overcrowding, poor sanitation and limited access to healthcare facilities and medication. This environment provides the perfect breeding ground for the growth and the transmission of scabies. (9, 10) In the UK, members of lower socioeconomic households/communities are more likely to experience some of the effects of relative poverty. These effects include inadequate access to health facilities and treatment, a poor level of hygiene, the sharing of unclean clothing, bedding or towels may facilitate transmission of scabies, malnutrition, and illiteracy. In addition, frequent population movements also facilitate the spread of the infestation. Though the exact prevalence of CS is unknown, it is thought to be rare; however, on several occasions, local epidemics of OS have originated from a single case of CS. (11)

There is a notable correlation between overcrowding and the prevalence of scabies. Overcrowding facilitates the rapid spread within a population. (10, 12) Additionally, the cases of scabies fluctuate depending on seasonal changes. A Russian study found that between the months of September and December, the fertility of scabies mites (and thus the incidence of scabies) was greater compared to the months of January to July (fertility index scores of 11.5 versus 8.9, respectively). (13) Further findings exemplified that scabies mite oogenesis arrest tends to be greater during the former half of the year, which subsequently leads to a seasonal decrease in the local scabies mite population which may cause a decreased incidence of scabies over the summer period. (13, 14) Finally, it is also important to note that a lack of healthcare and education regarding the condition and general hygiene inevitably mean that cases go untreated, contributing to its transmission and prevalence.
In the UK, the overall prevalence of scabies is 2.81 per 1,000 females and 2.27 per 1,000 males. Although relatively uncommon, children between the ages of 10 and 19 experience the highest infestation rates. There is a significantly greater infestation rate among females with a relative risk of 1.24 ($p < 0.001$) compared to males. (15)

Transmission

Scabies is a parasitic infection, caused by Sarcoptes scabiei var hominis (S. scabiei). These mites burrow into the stratum corneum of the epidermis of the skin, where the microenvironment is ideal for the parasite to remain and lay its eggs. This subsequently leads to an immune response from the host. This process is summarised in Figure 1.

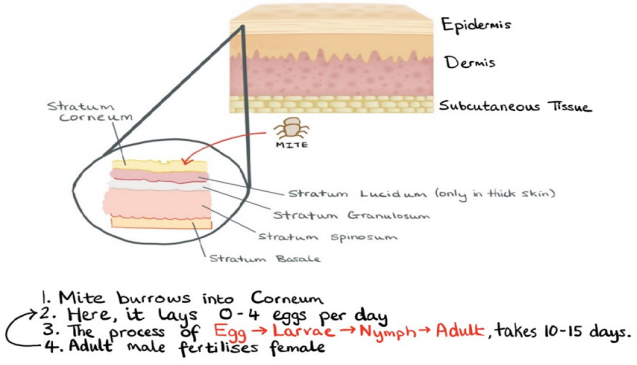

Figure 1:
The life cycle of S.scabiei and an illustration of the layers of skin and epidermis.

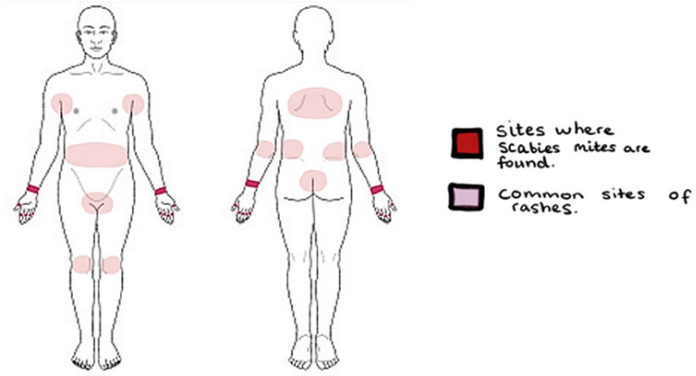

Figure 2:
Common sites S.scabiei mites are found, as well as sites of rashes.

Common sites of rashes and mite habitation can be seen in Figure 2; it includes areas such as the groin, shins, and armpits. (16) Extensive skin-to-skin contact with a person who has scabies is the most common form of transmission. Transmission may also occur via contact with items such as clothing, bedding, or towels that have been used by a person with scabies (more common in CS), or by having sexual intercourse with someone with the disease. (17) Based on this, it is understandable why those in LDCs experience the highest rates of prevalence, as transmission is exacerbated by overcrowded conditions that people may live in, as well as a general lack of sexual health awareness that may contribute to the spread of disease. Within 15 to 20 minutes of exposure, S. scabiei can infiltrate the skin and subsequently initiate its life cycle. The time taken for the onset of clinical manifestations after initial exposure may be up to eight weeks. (16) A correct diagnosis may be further delayed due to a lack of awareness from clinicians, as the signs and symptoms of scabies can mimic several other forms of skin disease, leading to a misdiagnosis. Further barriers to a rapid diagnosis include the lack of access to a hospital/GP and a lack of equipment that some practices may have to examine the patient. (18)

Clinical Manifestation and Diagnosis

One of the first symptoms of OS is a rash at the sites shown in Figure 2, and an intense pruritus, which typically worsens at night. At early stages of the condition (when scabies mites lay eggs in the skin), silvery lines with a dot at one end can be seen on the skin. As the rash spreads, it begins to present as tiny red spots. (17) A rash and pruritus are normally absent in CS; CS presents differently in that it presents more severely. There are many more mites in the skin, leading to CS being typically characterised by thick crusts of the skin, with a grey discolouration. (19) In CS, breached areas of the skin may exhibit erythema, which predisposes patients to secondary bacterial infection from Staphylococcus aureus and S pyogenes, (20) as well as causing skin infections like impetigo and worsening any existing eczema or psoriasis. (17)

Diagnosis of scabies is usually based on the history of the presenting symptoms. It is important to also take a social and family history in these cases, so that clinicians may understand if the condition has been spread via a family member. The presence of mite burrows in the skin are infrequently seen in OS, (7) so doctors may use other methods to achieve a definitive diagnosis. Methods may include dermatoscopy, but due to the equipment required this is infeasible in many remote areas, or a skin scrape, which involves scraping a blade coated with oil across a burrow and then examining the collected sample microscopically. Finally, scabies could also be diagnosed in remote communities via a 'burrow ink test:' a lesion suspected to be caused by scabies is covered in ink and then rubbed off the patient using alcohol. For a scabies-positive result, an ink tracking would remain in the burrows. (7)

Pathogenesis

Innate, humoral, and cellular responses are thought to play a significant role in the body's response to scabies. The immunological response is more apparent in patients with CS compared to OS, as the high mite count proportionally induces a stronger response. (21) A sufficient immune response is only generated 4-6 weeks after initial contact is made, partly due to genetic changes involved in epithelium development and partly because of the mite's ability to modulate gene expression via the expression of inhibitor proteins, thus delaying an innate immune response. (22) Once detected however, the body can overcome the condition, with assistance from medication. On the other hand, the doctor should feel the patient is sufficiently informed of the above to make a personalised decision. They should appreciate what the patient would consider a good outcome. They should understand what risks are important to that patient. They should have taken the opportunity to apply these factors to their recommended management plan. They should understand why a patient has come to a particular decision.

Innate immune response

The S. scabiei present in the stratum corneum is detected by two of the three complement-activating pathways: the classical and alternate pathway, which are activated by antigen-antibody complexes and endotoxins. (23) This leads to activation of the complement cascade, which produces the compounds C3a, C3b, C4a and C5a. The formation of these compounds eventually leading to the following outputs: chemotaxis of neutrophils and eosinophils to the parasite, mast cell activation, cell lysis and opsonisation of the parasite, which makes it more vulnerable to destruction by the immune system. The overall effect of these outputs is the priming of an adaptive immune response, which includes the mobilisation of a high number of eosinophils (responsible for the anti-helminth response) towards S. scabiei. When several of these eosinophils attach to the mites, they release compounds such as peroxidase, ribonuclease, and major basic protein, all of which contribute to killing the mites and their eggs. (24) S. scabiei have evolved to evade the complement cascade, via the production of two proteins: scabies mite serine protease inhibitor B3 and 4 (SMSB3 and SMSB3). (25) Both proteins bind directly to complement proteins, inhibiting their action in a way that all three complement-activating pathways are

disrupted. (26) This results in a temporary delay in the recruitment of eosinophils and a delay in the activation of the adaptive immune response. Consequently, S. scabiei can survive and multiply in the host longer.

Adapative immune response

The adaptive immune response must be launched to allow a host to overcome scabies. The role of the adaptive immune response becomes apparent when the numbers of Th2 lymphocytes increase in response to the parasite. The Th2 cell in turn secretes interleukins 4, 5 and 13 (IL-4, IL-5 and IL-13). Among other things, IL-4 promotes class switching of antibodies produced by plasma cells into different isotypes, notably, immunoglobulin E (IgE). IL-5 promotes the recruitment of eosinophils towards the site of infection, and IL-13 is responsible for expelling the parasite from the body once it has been killed. (27) There is an association between the presence of scabies and increased levels of antigen-specific IgE. (28)

IgE is a glycoprotein that specifically binds to target parasitic antigens. Effector functions of the antibody are normally mediated via the fragment crystallisable (Fc) region. It is this region which the eosinophils bind to, using the FcεRI receptors on their surface. Only when this binding occurs can the eosinophil begin to act on the parasite to kill it. (29) The antigen-binding fragment (FAB) of IgE binds to the corresponding receptor antigen on S. scabiei. Its high affinity results in numerous IgE antibodies coating S. scabiei. This is summarised in Figure 3. The interaction between the innate immune system and the humoral arm of the adaptive immune system allows the body to overcome the infestation.

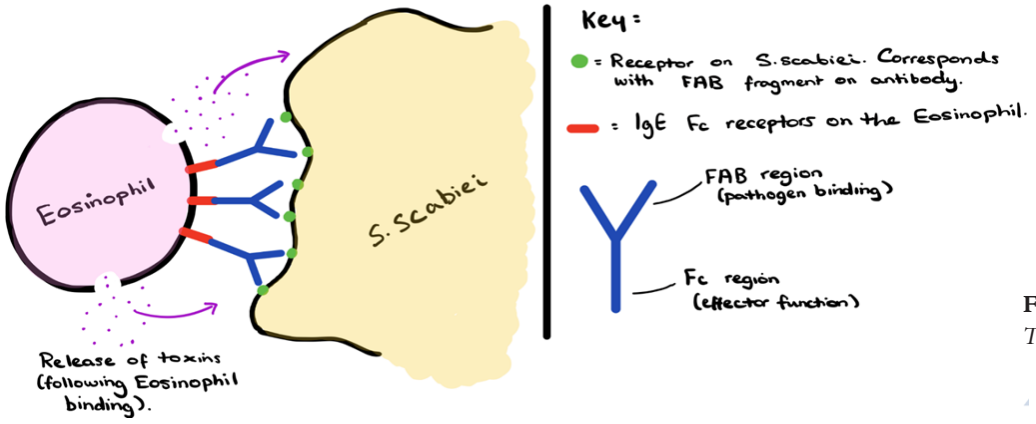

Figure 3:
The effector function of IgE.

Treatments and further developments

In the UK, the two most widely used treatments for scabies are Permethrin and Malathion. Both medications are to be applied topically and contain insecticides that kill the scabies mite. Of the two medications, Permethrin 5% cream is usually recommended as the first-line treatment; Malathion 0.5% lotion is administered if permethrin is ineffective. (30) Clinicians ask patients to apply the medication to their whole body, from the neck down, and leave it on for at least 8-10 hours (some treatments may also require a second application). (31) Clinicians should also recommend treatment for all the people the patient has been in close contact with, even if they show no signs of scabies infestation; this is due to the contagious nature of the condition.

The WHO recommends mass drug administration (MDA) as a method to treat and control outbreaks of scabies in LDCs. MDA involves treating every member within a defined population and location (unless specifically contraindicated) with scabicides, without individual diagnosis. In endemic areas, it aims to reduce transmission and alleviate symptoms of those infested. (32) A study conducted in rural Fiji tested the effectiveness of MDA, using Permethrin as medication. The trial was conducted in 2012 for 12 months and involved 2051 participants in total. It found that those who underwent MDA had a statistically significant 62% reduction in cases of scabies from baseline. (33) Though this study, along with others, suggest that MDA is effective in LDC, a limitation to this model regards population movement between an area which had been treated with MDA to scabies-prevalent areas, which may lead to re-infestation.

As mentioned above, there are several difficulties in promptly diagnosing scabies in LDCs. However, recent advancements in diagnosis may assist this issue. A study by Jayaraj and colleagues investigated the potential of using IgE antibodies which are specific to recombinant Sar s 14.3 (rSar s 14.3), a major antigen of scabies. This immunological assay was quantified and assessed. The diagnostic efficiency of rSar s 14.3 detecting active scabies infestation was extremely high, with a 100% sensitivity and 93.75% specificity to patients with scabies. This shows great potential as a test for scabies. (34) Nonetheless, it is still in its early stages of development, and appears to be resource intensive, which may be a problem for resource deficit countries.

CONCLUSION

Scabies has been brought back to the attention of clinicians worldwide when the WHO categorised it as one of 17 NTDs. Although not usually life-threatening, scabies can cause symptoms which can reduce a person's quality of life. Undiagnosed, scabies may lead to serious complications such as secondary skin sepsis, as well as devastatingly vast transmission in densely populated areas. Problems in LDCs include the difficulty surrounding diagnosis due to a lack of awareness about the condition, as well the scabies mite's adaptations to evade the immune system. Despite progress in the management of the condition, the pathophysiology and transmission of the condition are only partly understood. The rise of resistance to current scabicides is indicative of the need for newer treatments, especially within resource poor communities.

REFERENCES

1. World Health Organisation. Neglected tropical disease. Genva, Switzerland: WHO; 2013 [accessed 04 Feb 2020]. Available at: https://www.who.int/neglected_diseases/diseases/en.

2. Molyneux D. Neglected tropical diseases. Community Eye Health. 2013;26(82):21–24.

3. Molyneux D. "Neglected" diseases but unrecognised successes – challenges and opportunities for infectious disease control. The Lancet. 2004;364:380-383.

https://doi.org/10.1016/S0140-6736(04)16728-7

4. Rübsam M, Esch M, Baum E, Bösner S. Diagnosing skin disease in primary care: a qualitative study of GPs' approaches: Table 1. Family Practice. 2015;32(5):591-595.

https://doi.org/10.1093/fampra/cmv056

PMid:26160890

5. Awandalla F, Rosenbaum D, Camacho F, Fleischer A, Feldman S. Dermatologic disease in family medicine. Family Medicine. 2008;40(7):507-511.

6. Boer M, Duchnik E, Maleszka R, Marchlewicz M. Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function. Advances in Dermatology and Allergology. 2016;1:1-5.

https://doi.org/10.5114/pdia.2015.48037

PMid:26985171

7. Banerji A. Scabies. Paediatrics & Child Health. 2015;20(7):395-398.

https://doi.org/10.1093/pch/20.7.395

PMid:26527041

8. Burkhart CG, Burkhart CN, KM Burkhart KM. An epidemiologic and therapeutic reassessment of scabies. Cutis. 2000;65:233-240.

9. Terry B. Sarcoptes scabiei infestation among children in a displacement camp in Sierra Leone. Public Health. 2001;115(3):208-211.

https://doi.org/10.1016/S0033-3506(01)00445-0

10. Pruksachatkunakorn C, Wongthanee A, Kasiwat V. Scabies in Thai orphanages. Pediatrics International. 2003;45(6):719-723.

https://doi.org/10.1111/j.1442-200X.2003.01811.x

PMid:14651549

11. Holness D. Scabies in chronic health care institutions. Archives of Dermatology. 1992;128(9):1257-1260.

https://doi.org/10.1001/archderm.128.9.1257

PMid:1519942

12. Walton S, Dougall A, Pizzutto S, Holt D, Taplin D, Arlian L et al. Genetic epidemiology of Sarcoptes scabiei (Acari: Sarcoptidae) in northern Australia. International Journal for Parasitology. 2004;34(7):839-849.

https://doi.org/10.1016/j.ijpara.2004.04.002

PMid:1515776

13. Sokolova TV, Radchenko MI, Lange AB et al. The seasonality of scabies morbidity and the fertility of the itch mite Sarcoptes scabiei de Geer as an index of the activity of a population of the causative agent. Vestn Dermatol Venerol. 1989;(11):12–15.

14. Liu J, Wang H, Chang F, Liu Y, Chiu F, Lin Y et al. The effects of climate factors on scabies. A 14-year population-based study in Taiwan. Parasite. 2016;23:54.

https://doi.org/10.1051/parasite/2016065

PMid:27905271

15. Lassa S, Campbell M, Bennett C. Epidemiology of scabies prevalence in the U.K. from general practice records. British Journal of Dermatology. 2011;164(6):1329-1334.

https://doi.org/10.1111/j.1365-2133.2011.10264.x

PMid:21574970

16. Centres for Disease Control and Prevention. Scabies. Atlanta, Georgia: CDC; 2010 [accessed 13th February 2020]. Available at: https://www.cdc.gov/parasites/scabies/disease.html.

17. Scabies. nhs.uk. London: NHS; 2017 [accessed 2 April 2020]. Available from: https://www.nhs.uk/conditions/scabies.

18. Hengge UR, Currie BJ, Jager G, et al. Scabies: a ubiquitous neglected skin disease. Lancet Infect Dis. 2006;6:769–779.

https://doi.org/10.1016/S1473-3099(06)70654-5

19. Centres for Disease Control and Prevention. What is crusted (Norwegian) scabies? Atlanta, Georgia: CDC; 2010 [accessed on 15th February 2020]. Available at: http://www.cdc.gov/parasites/scabies/gen_info/faqs.html#crusted.

20. Brook I. Microbiology of secondary bacterial infection in scabies lesions. Journal of clinical microbiology. 1995;33(8):2139-2140.

https://doi.org/10.1128/JCM.33.8.2139-2140.1995

PMid:7559963

21. Roberts LJ, Huffam SE, Walton SF, Currie BJ. Crusted scabies: Clinical and immunological findings in seventy-eight patients and a review of the literature. J Infect. 2005;50:375-81.

https://doi.org/10.1016/j.jinf.2004.08.033

PMid:15907543

22. Morgan M, Arlian L, Markey M. Sarcoptes scabiei Mites Modulate Gene Expression in Human Skin Equivalents. PLoS ONE. 2013;8(8):e71143.

https://doi.org/10.1371/journal.pone.0071143

PMid:23940705 PMCid:PMC3733868

23. Walton S, Pizzutto S, Slender A, Viberg L, Holt D, Hales B et al. Increased Allergic Immune Response to Sarcoptes scabiei Antigens in Crusted versus Ordinary Scabies. Clinical and Vaccine Immunology. 2010;17(9):1428-1438.

https://doi.org/10.1128/CVI.00195-10

PMid:20631334 PMCid:PMC2944463

24. Anthony R, Rutitzky L, Urban J, Stadecker M, Gause W. Protective immune mechanisms in helminth infection. Nature Reviews Immunology. 2007;7(12):975-987.

https://doi.org/10.1038/nri2199

PMid:18007680 PMCid:PMC2258092

25. Mika A, Reynolds S, Pickering D, McMillan D, Sriprakash K, Kemp D et al. Complement Inhibitors from Scabies Mites Promote Streptococcal Growth – A Novel Mechanism in Infected Epidermis? PLoS Neglected Tropical Diseases. 2012;6(7):e1563.

https://doi.org/10.1371/journal.pntd.0001563

PMid:22815998 PMCid:PMC3398963

26. Mika A, Reynolds S, Mohlin F, Willis C, Swe P, Pickering D et al. Novel Scabies Mite Serpins Inhibit the Three Pathways of the Human Complement System. PLoS ONE. 2012;7(7):e40489.

https://doi.org/10.1371/journal.pone.0040489

PMid:22792350 PMCid:PMC3394726

27. Bao K, Reinhardt R. The differential expression of IL-4 and IL-13 and its impact on type-2 immunity. Cytokine. 2015;75(1):25-37.

https://doi.org/10.1016/j.cyto.2015.05.008

PMid:26073683 PMCid:PMC5118948

28. Bhat S, Mounsey K, Liu X, Walton S. Host immune responses to the itch mite, Sarcoptes scabiei, in humans. Parasites & Vectors. 2017;10(1).

https://doi.org/10.1186/s13071-017-2320-4

PMid:28797273 PMCid:PMC5553898

29. Fitzsimmons C, Falcone F, Dunne D. Helminth Allergens, Parasite-Specific IgE, and Its Protective Role in Human Immunity. Frontiers in Immunology. 2014;5.

https://doi.org/10.3389/fimmu.2014.00061

30. Scabies - Diagnosis and treatment - Mayo Clinic. Rochester, Minnesota: Mayo Clinic; 2020 [cited 3 April 2020]. Available from: https://www.mayoclinic.org/diseases-conditions/scabies/diagnosis-treatment/drc-20377383.

31. Scabies symptoms and treatments. Nhsinform.scot. Scotland: NHS; 2020 [cited 3 April 2020]. Available from: https://www.nhsinform.scot/illnesses-and-conditions/skin-hair-and-nails/scabies.

32. Webster J, Molyneux D, Hotez P, Fenwick A. The contribution of mass drug administration to global health: past, present and future. Philosophical Transactions of the Royal Society B: Biological Sciences. 2014;369(1645):20130434.

https://doi.org/10.1098/rstb.2013.0434

PMid:24821920 PMCid:PMC4024227

33. Romani L, Whitfeld M, Koroivueta J, Kama M, Wand H, Tikoduadua L et al. Mass Drug Administration for Scabies Control in a Population with Endemic Disease. New England Journal of Medicine. 2015;373(24):2305-2313.

https://doi.org/10.1056/NEJMoa1500987

PMid:26650152

34. Jayaraj R, Hales B, Viberg L, Pizzuto S, Holt D, Rolland JM, et al. A diagnostic test for scabies: IgE specificity for a recombinant allergen of Sarcoptes scabiei. Diagn Microbiol Infect Dis. 2011;71(4):403-7.

https://doi.org/10.1016/j.diagmicrobio.2011.09.007

PMid:22018936

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Reflections

The case for a wellbeing representative in medical school

REFLECTIONS

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INTRODUCTION

It is known that medical students' and other healthcare professionals' mental and general wellbeing are frequently impacted by stressors and pressure. (1) In response, the General Medical Council (GMC) initiated a UK-wide review in 2018 on the causes of poor wellbeing, which concluded that the medical community needs to feel empowered to express concerns and speak up. (2) Subsequently, this led to development and increasing awareness of wellbeing services across universities.
We are three clinical medical students who aim to provide an insight into the student-generated wellbeing initiatives which have been set up and supported by our medical school. In an era where the COVID-19 pandemic breeds uncertainty and anxiety amongst medical students, wellbeing initiatives are vital to implement, sustain and fund. We hope this reflection on our own experiences can provide other universities with a perspective on what they can implement at their respective medical schools.

Wellbeing Provision by the Medical School

The medical school offers wellbeing services via the student services centre through qualified staff, and wellbeing assistants. Consultations can be booked, or students can make use of the drop-in services during specified hours. However, in the height of the COVID-19 pandemic, remote consultations were trialled to support students. However, such consultations were limited due to technological restrictions and staff now working from home. Whilst the use of remote consultations is a useful substitute, given the circumstances, it is essential that in-person consultations are available where possible. There are various advantages to in-person consultations, such as removal of any 'barriers' like poor internet connection. In such vulnerable situations, being able to have no interruptions in conversation regarding wellbeing, can make a significant difference in supporting individuals.

A Wellbeing Representative

While the medical school provides staff-led wellbeing support, the student body also has another layer of support for student wellbeing. The 'Wellbeing Representative' is an elected position at the Curriculum and Wellbeing Committee (CAWC) at our university. It is a student-led committee which acts as a bridge between the staff and students. The Wellbeing Representative volunteers to become the voice for medical students' wellbeing. Riaz, the CAWC 2019-20 Wellbeing Representative, shared his insights into the role:

"The role is varied, challenging but ever-so rewarding. Primarily my responsibilities involve organising our GMC recognised 'FeelBright' campaign, a series of lectures and small group sessions aimed at helping students manage mental health issues and reduce stigma. This was introduced in the early 2000s. Moreover, I oversee organising 'Wellbeing Week' for students from all courses which are based in the medical school. However, my role further extends to student representation, relaying concerns, and student ideas to staff groups in order to improve student wellbeing. To do this, I ensure that I am approachable to students and peers, by listening to their concerns and signpost students to the appropriate university services."

'FeelBright' Campaign

The 'FeelBright' campaign aims to increase awareness and understanding of anxiety and depression, reduce stigma and offer a clear support pathway. The campaign is run by CAWC, with the help of other students and wellbeing staff. There are three core components to the campaign: the 'FeelBright' booklet, a lecture to Year 1 students, and small group teaching sessions for Year 2 students. It tries to combat students' thinking that they will be 'deemed incompetent' if they seek help for anxiety, depression, or any other mental health problem.

Extending 'Wellbeing Week' activities into a year-round event could complement the 'FeelBright' campaign. Moreover, being able to deliver the campaign virtually is the plan for the 2020-21 academic year, to accommodate the continued disruption to curricula caused by COVID-19. Consistent and repetitive exposure of the message to students could have a greater impact and would help keep wellbeing at the forefront of conversation. Through conversing with the cohort, we have found that a number found the 'FeelBright' booklet difficult to access and it would discourage them from using it. Therefore, we raised the idea of making the booklet available through the existing University of Birmingham app. Although finance and time have proved to be hurdles, we hope that this is an avenue that could be pursued further.

Wellbeing Week

In addition to the FeelBright campaign, 'Wellbeing Week' is another responsibility of the Wellbeing Representative. 'Wellbeing Week' is a CAWC and Medical Society (MedSoc) collaboration based on the NHS '5 Steps to Mental Wellbeing'. (3) This week consists of activities that work towards the steps of connecting with other people, being physically active, learning new skills, giving to others and mindfulness. 'Wellbeing Week' has run for the past two academic years. The first was held in March 2019, a busy period in the medical school where students would be heavily focused on revision. In 2020, 'Wellbeing Week' was held in February, two months before end of year exams, in a time where students may feel overwhelmed with exams looming and a feeling of unpreparedness. This week aims to remind to students that there is always time to take care of their own wellbeing. This year, there were a plethora of activities which were run by fellow students, from charitable acts, to arts and exercise. Ultimately, this creates a community of students dedicated to supporting one another. Figure 1 shows a poster of the activities that were held during the Wellbeing Week in 2020.

Figure 1

Activities poster from Wellbeing Week 2020

Thus far, the Wellbeing Week has had positive responses from students (Figure 2). Although responses have been positive, it is also important to consider ways of improving the service and the awareness of the importance of wellbeing. It would be useful to extend such privileges throughout the year, by providing different wellbeing activities on a weekly basis; both in person and virtually. This enables a structure that students can implement into their schedules as a method to relieving stress from their studies. Subsequently, achievable initiatives and ideas can be trialled and implemented by the university. Given the impact of COVID-19, this is the prime time for innovation and rejuvenation of wellbeing services. Providing an online platform where students can anonymously express concerns regarding their course or exams can help overcome the logistics where some students are hesitant to speak up in person.

Figure 2

Feedback from Wellbeing Week 2020

Overall, as initiators and receivers of this wellbeing initiative at our university, we have found this to be a promising method of relieving stress, promoting wellbeing and minimising the stigma surrounding mental health. We believe initiatives like the above are a fantastic way for students to get together as a community to communicate and normalise their feelings.

The Evolution in the Wellbeing Representative Role

Although some initiatives are great at raising awareness at a given time in the academic year ('Wellbeing Week'), we believe it is imperative to promote wellbeing throughout the year. This is of greater importance now due to the current affairs. COVID-19 has impacted students' education greatly and with the huge uncertainty on how students will progress through the years or gain the appropriate clinical exposure, it is likely this pandemic will impact students' wellbeing. Moving forward, there needs to be a much greater agenda in supporting student wellbeing, innovation and student-led ideas, as these are instrumental in advancing medical student wellbeing.

We believe having access to a Wellbeing Representative is extremely beneficial for the student community. Having a medium that ensures all our wellbeing concerns are heard, enables the university to tailor appropriate resources to our needs at that time. The role of the representative is to ensure every student, irrespective of their year group, is comfortable in approaching them as a link for further support. The use of regular emails, posts to relevant course pages, wellbeing posters, and events supports a welcoming environment. The Wellbeing Representative is a member of CAWC and so has only been made to cater for undergraduate and postgraduate students on the MBChB course. However, other courses are not so fortunate to have such a support structure. In response to this, 'Wellbeing Week' was launched in collaboration with the MedSoc to support other healthcare courses.

Student involvement in the organisation and provision of wellbeing services in higher education is not novel, but it has been an area of recent development. For instance, Imperial College London have University Wellbeing Representatives. (4) However, we have been unable to locate other published literature outlining other UK medical schools with an appointed Wellbeing Representative for their school. The University of Birmingham also values the wellbeing of staff, and the "Employee Advice and Listening Service" is a prime example. It is a professional service aiming to guide staff through personal or work-related problems. Staff also have access to counselling via an external provider. (5)

Despite consistently positive feedback, there is scope for improvement. At present, there is a single wellbeing representative for both undergraduate and graduate-entry medical students of all years. We believe that progressing to a representative for each year group in both groups would ensure better representation from the cohort and the programme.

CONCLUSIONS

Overall, we hope that through our reflective piece, we have highlighted the importance of wellbeing amongst medical students, and how essential a wellbeing representative can be in the student community. We hope students from other unions will take a moment to equally reflect on the representation of wellbeing in their school or university and think, what can we do to try and improve this? We hope our reflection on the model, devised at the University of Birmingham, provides insight into what you could implement within your own student unions.

REFERENCES

1. Kulsoom B, Afsar NA. Stress, Anxiety, and Depression among Medical Students in a Multiethnic Setting. Neuropsychiatric Disease and Treatment. 2015;11:1713-1722.

https://doi.org/10.2147/ndt.s83577

PMid:26213470 PMCid:PMC4509544

2. West M, Coia D. Caring for Doctors, Caring for Patients: How to Transform UK Healthcare Environments to Support Doctors and Medical Students to Care for Patients. London: GMC UK; 2019 [accessed 7 Jun 2020]. Available from: https://www.gmc-uk.org/-/media/documents/caring-for-doctors-caring-for-patients_pdf-80706341.pdf.

3. NHS. 5 Steps to Mental Wellbeing. London: NHS; 2019 [accessed 7 June 2020]. Available from: https://www.nhs.uk/conditions/stress-anxiety-depression/improve-mental-wellbeing.

4. Imperial College Union. Academic & Wellbeing Representatives. London: Imperial College Union; 2020 [accessed 6 August 2020]. Available from: https://www.imperialcollegeunion.org/academic-wellbeing-representatives#:~:text=The%20Wellbeing%20Reps%20are%20responsible,our%20Rep%20Network%20Pathways%20diagram.

5. University of Birmingham Human Resources. Wellbeing Services. Birmingham: University of Birmingham; 2020 [accessed 6 August 2020]. Available from: https://intranet.birmingham.ac.uk/hr/wellbeing/workhealth/index.aspx.

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