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FOREWORD

The School of Pharmacy and Pharmaceutical Sciences, Cardiff University, is the only school of pharmacy in Wales and is one of the top schools of pharmacy in the UK. Our students graduate well-prepared and satisfied, as seen by the consistently high pass rate in the pharmacist registration examination and high ranking in the National Student Survey respectively.

In addition to supporting individual pharmacists in their initial and ongoing education and development, the School is active in research that has been independently judged to be predominantly of international standing, more than half of which is recognised as world-leading or internationally excellent and with many interdisciplinary and external collaborators. Research at the School encompasses medicinal chemistry, drug delivery and microbiology, pharmacology and physiology, and pharmacy practice and clinical pharmacy, and it impacts on healthcare and pharmaceutical sciences throughout the UK and the world. Further information on the School's research activities and degree programmes, along with contact details for academic staff can be found at http://www.cardiff.ac.uk/phrmy.

At the Cardiff School of Pharmacy and Pharmaceutical Sciences, the combination of these strengths allows us to successfully deliver research-led learning and teaching. All of our MPharm students undertake a significant, independent Masters level research project in the final year of the four-year degree, and present and defend their research. The high numbers of well-qualified UK, EU and international students that we attract to our postgraduate diplomas and degrees also contribute significantly to our research output.

This is the 21st year in which we have published the abstracts of our students' research. Within this publication the student is the first named author, and collaborators and supervisors follow. An alphabetical list of authors appears in the index.

Many thanks to our colleagues for their assistance in collating this book.

Rhys Thomas, Dean Routledge & Justine Jenkins
August 2023

Data Analysis of the Co-Ingestion of Tricyclic Antidepressants with Other Agents and Associated Demographics

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Tricyclic antidepressants (TCA) are a class of antidepressants known to be toxic in overdose due to a narrow therapeutic window and a short half-life.[1] However, they are still readily prescribed for depressive and non-depressive conditions.[2] This study looked at the demographics of TCA polypharmacy poisoning cases recorded on UKPID, TCA prescribing trends and related mortality data in England and Wales.

TCA polypharmacy overdose enquiries made to the National Poisons and Information Service (NPIS) by healthcare professionals were recorded on the UK Poisons and Information Database (UKPID). The NPIS provided 2749 enquiries, after screening according to inclusion criteria, 1651 cases remained for further trend analysis. Prescribing data was provided All Therapeutic All Wales Therapeutic and Toxicity Centre (AWTTC) and mortality data by the Office of National Statistics (ONS).

Amitriptyline was the most common TCA involved in polypharmacy overdoses (n=1413) and females were the most prominent gender (n=984). Individuals aged 30 to 39 were the most commonly reported age group (n=310) and intentional overdose was the most frequently reported circumstance (n=1120). Therapeutic errors were the most frequent circumstance reported (n=113) among people aged 70+. From 1993 to 2020, the number of deaths involving a TCA and alcohol decreased.

Females were disproportionately more likely to have an accidental or therapeutic overdose ($p<0.01$) and age was found to have a significant effect on the circumstance reported ($p<0.01$). Overall, prescribing of TCAs has increased from 2014 to 2020 but the number of cases reported to the NPIS has decreased, suggesting TCA prescribing has shifted towards non-depressive disorders. More males died due to co-ingestion of a TCA and alcohol, despite females most likely to have co-occurring alcoholism and depression.[3] Reports indicate a deterioration in mental health since the beginning of the pandemic, hence further analysis from 2020 onwards would be more reflective of current trends.

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Exploring MPharm IV student views on blended learning and its impact on preparedness for Oriel assessments and Pharmacy Practice

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The COVID-19 pandemic had a significant impact on Higher Education. Cardiff University School of Pharmacy implemented a blending learning pedagogical approach combining a mixture of online and in-person teaching.[1, 2] There is limited published research if this new way of learning is effective in preparing pharmacy students for the workplace environment.[3] Foundation trainee pharmacists must display the knowledge, skills and attitudes for practice and the Oriel recruitment assessments assess some of these professional attributes.[4] This study aimed to explore the perceptions of Cardiff MPharm IV students on preparedness for Oriel assessments and Pharmacy Practice using a blended approach.

Following ethics approval, three researchers conducted thirteen one-to-one semi-structured interviews. Each interview was video taped with consent, and then transcribed. The data collected was shared amongst all researchers and independent analysis was undertaken using the code and retrieve method, producing a thematic framework.

Five main themes were identified: engagement with blended learning, perceived challenges, preparation for Oriel assessments, pharmacy practice and transitioning to foundation training. Blended learning enhanced transferable skills such as leadership and adaptability whilst the main challenge was communication,

particularly in modules with limited in-person teaching. The majority of participants felt confident in performing calculations, dispensing and communicating with patients but less prepared carrying out pharmaceutical care plans and multi-disciplinary working.

The study concluded blended learning although heterogeneous has the potential to stimulate effective learning. The degree provides students with the knowledge and skills for pharmacy practice but the extent of preparedness differed amongst students. To address this, increasing clinical exposure, vacation placements, utilise more online software and expanding inter-professional collaboration sessions should be considered. Future studies include research to standardise blending learning, a longitudinal follow up study and distributing a questionnaire to MPharm IV students based on the themes from this study to cover a larger population.

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Gabapentinoids in the treatment of phantom limb pain: a rapid systematic review

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According to the European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of peripheral arterial diseases, patients experiencing severe necrosis or infections may need major amputation as a last option to prevent any further complications. Amputee patients may develop phantom limb pain (PLP). This is the pain that is perceived from a limb that is no longer present. studies show that it is prevalent in 60-80% of amputee cases and can last for years in some patients.[1]

A rapid review was undertaken to find literature in order to determine when gabapentinoids should be reviewed in phantom limb pain. 12 papers were identified through database screening

Three randomised control trials were found and numerous retrospective cohort studies were used in this review

Prescription and drug monitoring of gabapentinoids in phantom limb pain is a very niche area. Currently there is no relevant primary research to indicate or give guidance on how these drugs should be managed. Future work should include looking into this area, maybe in an observational manner or cohort studies, rather than doing a literature review as data is outdated at the moment. Gabapentinoids should also be researched to truly test their efficacy in phantom limb pain. Although the aim for this review couldn't be met, the outcome is that there is a growing need for healthcare professionals to monitor for abuse factors especially when prescribing drugs like pregabalin and gabapentin which can cause a whirlwind of issues if not managed correctly

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Cysteamine as a potential novel antibiotic: A rapid review of the literature

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Clinically, bacterial infections are managed by antibacterial agents, which either kill or inhibit the growth of bacteria.[1] However, their efficacy has declined due to the emergence of antibacterial resistance as a result of antibacterial misuse. If bacterial infections are left untreated, they can lead to life threatening consequences such as sepsis.[2] Therefore, multi-drug resistance remains one of the most alarming issues and the

development of novel antibacterial agents is essential to overcome resistance. Cysteamine is currently licenced for the treatment of cystinosis which is a rare metabolic disease in which cysteine crystals accumulate in the organs, however the drug has also shown to have potent antibacterial and mucolytic activity.[3] The main objective of this review is to identify whether cysteamine can be a repurposed drug as an antibacterial agent and to assess whether clinical trials should be conducted to assess the suitability of cysteamine as an antibacterial agent.

The following terms were applied in the search process of publications "cysteamine; antibacterial and MIC". In addition, all publications reviewed were extracted from four databases: PubMed, Embase, Medline and SCOUPS. To ensure that all data included was up to date only papers published in the past 8 years were included in the review. The final papers included in the review were selected according to the inclusion criteria, all publications were critically appraised thereafter.

According to the results from the publications cysteamine has antibacterial activity via a redox mechanism of action by generating reactive oxygen species which disrupts the metabolism within bacterial cells consequently inhibiting bacterial growth.[4] Therefore, cysteamine poses a bactericidal mechanism of action.

After reviewing all the publications in the review, cysteamine can be a drug repurposed as an antibacterial agent potentially for respiratory tract infections in cystic fibrosis patients due to its mucolytic properties, which allows a better penetration of the drug into the respiratory tract. Hence, clinical trials should be conducted on patients suffering from respiratory tract infections in cystic fibrosis patients to generate an antibacterial agent with an improved efficacy and pharmacological profile.

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Cell Transplantation for Neurodegenerative Disorders: A Systematic-Rapid Review

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Traumatic brain injury occurs when an area of the brain is injured, and brain function is lost. The most common causes of traumatic brain injuries include assault, sport injuries and vehicle accidents. There are no cures for traumatic brain injuries[1]; nevertheless, one potential therapeutic intervention is transplanting cells to repair the injury site. However, the majority of grafted cells die post-transplantation, the reasons for which are not well-elucidated.

The aim of this project was to systematically analyse pre-clinical studies in an attempt to shed light on why cells die post-transplantation and investigate factors that affect cell survival. A systematic rapid review of the literature surrounding cell transplantation to the brain was performed. Three databases were searched, and the studies found were screened by four individuals against inclusion and exclusion criteria which was chosen to best match why cells die. After a consensus was agreed by all researchers for all included papers, the final number of studies bought forward for inclusion in this review was 21.

Neural stem cells were predominantly used in included studies, with one study reporting its migration and engraftment in the brain 20-weeks post-transplantation.[2] However, other studies reported poor survival when transplanted alone, for example, survival of cells when a PuraMatrix hydrogel was used was greater than when cells were transplanted alone.[3] Aside from using hydrogels, genetic modification was another intervention used, such as genetically modifying neural progenitor cells to secrete synthetic, human multineurotrophin (MNTS1), resulting in an increased survival of cells 6-weeks post-transplantation.[4]

Cell death has been suggested to occur due to a variety of processes; however, a solid conclusion cannot be drawn, which showcases the need for further research and a more standardized approach to investigate why cells die and to systematically assess cell types and interventions that're relevant for the survival of cells post-transplantation.

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Using Antivirals to tackle Post-Transplant CMV: a rapid literature review

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Cytomegalovirus, or CMV, is a prevalent herpesviridae virus that presents as a latent infection in immunologically healthy people but can have disastrous effects in the immunosuppressed. CMV can harm many organs in the body and can cause allograft rejection in transplant recipients.[1]

The aim of this review is to analyse the efficacy of antiviral therapy in the treatment of post-transplant CMV and to assess how altering treatment strategy can tackle the problems that arise with antiviral therapy such as antiviral resistance and toxicity.

The chosen databases Medline, Embase and Scopus were used to search, filter, and extract appropriate research articles into Endnote. Filtering strategies involved choosing keywords, combining search terms, and adding date limits. Search results were analysed according to inclusion and exclusion criteria and the paper extraction process was summarised using a PRISMA diagram.

18 papers were included in the final analysis. All relevant data was extracted into a table. Joanna Briggs Institute (JBI) critical appraisal tools were used to ensure minimum bias in the chosen papers. However, the papers were heavily saturated with cohort studies where record keeping was dependent on third-party members, therefore it is possible some data is missing from these studies. Although ganciclovir (GCV) has been used as 'gold standard' initial therapy previously, antiviral resistance is now an issue that requires attention.[2]

GCV has been effective in treating CMV, but emerging GCV-resistance stresses the need for new antivirals or updated treatment strategies. Letermovir shows great potential in being used for the treatment of CMV in solid-organ transplant recipients. Its benefits seem greater through combination therapy with VGCV.[3] Of the more recent antivirals, Brincidofovir and Maribavir were less effective as treatment in the data collected but this uncertainty can be due to small patient population in the reports presented. Further research is required to come to definite conclusions that may lead to application in practise.

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A rapid review on the effects of *Staphylococcus aureus* biofilm in the wound healing of diabetic foot ulcers.

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Almost 80% of lower limb amputations are caused by diabetic foot ulcers.[1] *Staphylococcus aureus* is one of the most common pathogens isolated from diabetic foot ulcers and known to express genes that instigate biofilm formation.[2] Research has shown that biofilms evade bacterial eradication from antibiotics and host

defence mechanisms.[1-3] Biofilms are identified in different types of infections including chronic wounds,[3] displaying higher resistance to antibiotics compared to free-floating bacteria.[1, 3] This rapid review aims to review and critically analyse available literature to determine how biofilms of the bacterial species *S. aureus* affect wound healing in diabetic foot ulcers.

Scopus, Web of Science, Pubmed and Google Scholar were used to gather relevant and eligible publications from the year 2010-2020. The results were imported into EndNote-X9 and screened against a constructed eligibility criterion. PRISMA flow diagram was used to record the number of papers at each stage of screening.[4] Quality of the papers was critically analysed based on the data extracted from the articles and with the use of critical appraisal tools.

37 papers were included in the review out of 3720 papers initially identified. Results demonstrated that toxin secretion of *S. aureus* strains was enhanced in biofilms resulting to macrophage dysfunction. Furthermore, *S. aureus* biofilm creates a hypoxic environment to impair cell function, increases inflammation of wounds and decreases the likelihood of wound repair. In addition, *S. aureus* biofilm formation is enhanced in diabetic foot ulcers leading to increased antibiotic resistance.

Consequently, *S. aureus* biofilms delay wound healing in diabetic foot ulcers by primarily hindering the normal progression of wound repair. Diabetic foot ulcers are stalled in the early stages of the wound healing process and through inefficient macrophage phagocytosis and antibiotic tolerance, it leads to further biofilm formation.

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'How does anthracycline chemotherapy affect calcium signalling of the cardiac ryanodine receptor to bring about cardiotoxic effects?' – A Rapid Review

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Anthracyclines are a large class of cytotoxic agent used to treat a variety of cancers.[1] However, their use is often hindered by their cardiotoxic side-effects.[2] It has been previously proposed that cardiotoxicity is caused by production of reactive oxygen species (ROS), mitochondrial dysfunction and calcium homeostasis dysregulation.[3] However, the mechanism by which anthracyclines affect calcium signalling remains unclear. This review aims to investigate the mechanism by which this occurs, investigating the involvement of the cardiac ryanodine receptor (RyR2) in dysfunctional calcium release.

The databases Embase, Medline and Scopus were used to search for literature. The umbrella terms "anthracycline chemotherapy", "ryanodine receptor" and "cardiotoxic effects" were used to identify papers. Papers identified were screened for eligibility, and included studies were assessed for risk of bias. Relevant data from included studies were extracted to identify key mechanistic data.

A total of 210 papers were identified of which 13 were deemed suitable and included in this rapid review. This review found that anthracyclines affect RyR2 function through six central mechanisms, including: alterations in calcium release, biphasic alterations in calcium release, direct interaction with RyR2, ROS-mediated oxidation of RyR2, phosphorylation of RyR2 and interaction with Calsequestrin 2.

This rapid review provides limited evidence that the mechanism by which anthracyclines bring about cardiotoxicity is likely to be influenced by all the mechanisms proposed and cannot be attributed to a singular mechanism. More contemporary and robust research is required to evaluate the full contribution of these mechanisms to cardiotoxicity from anthracycline use. This review also suggests that this mechanistic data would provide useful insight into discovery of new treatments for anthracycline-induced cardiotoxicity.

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An Investigation into the experiences of formal care workers within domiciliary care in Wales regarding medicines support: A qualitative analysis

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Medicines support including the administration, ordering, and disposal of medicines is now an integral part of the service provided by domiciliary care.[1] This service is used by older adults who are more vulnerable to harm from medication errors due to age-related changes in their pharmacokinetics.[2] Therefore, it's important to investigate the views of care workers whether they feel confident with the training they received. This research aimed to explore the views and experiences of home care workers in Wales with regards to their role in medicines management and the potential challenges and issues they face. Overall aims to improve the safety and efficacy of practice.

A qualitative approach utilising semi-structured interviews was used due to the exploratory nature of the study. Non-purposive sampling was used to recruit the participants who were all from the same health board. Interviews were audio-recorded then transcribed verbatim. The interviews were then thematically analysed and major themes and subthemes were identified.

Four main themes were identified. Lack of knowledge of both medication policies and medications, communication barriers between health care professionals and the impact this has on discharges, the importance of continuity of care and building relationships with service users, and lastly medication administration records as the key focus of training.

This study concluded that there is not a consistent policy across wales for medicines management. Additionally, the study was unable to conclusively determine if the policy is reflected in practice. The results from his research suggest there is a lack of knowledge of medicines, and further training would be beneficial. Communication barriers between health care professionals were found to be the biggest issue in home care. Further research is required to explore the views of medicines management in-home care nationwide with the additional perspective of care managers.

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Treatment of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) – Rycal JTV519 as a novel therapeutic compound

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CPVT is a form of ventricular tachycardia, induced by emotional stress or physical exercise, which can deteriorate into ventricular fibrillation. Cardiac ryanodine receptor (RyR2) mutations are responsible for over 50% of CPVT cases[1,2], which cause spontaneous Ca^{2+} release out of the sarcoplasmic reticulum (SR) during diastole, causing delayed afterdepolarisations (DADs) and abnormal heart beats. JTV519 is proposed to stabilise RyR2, preventing such Ca^{2+} release, thus regulating arrhythmia[3]. However, the mechanism of JTV519 Ca^{2+} regulation remains controversial[2] and aims to be evaluated in this review.

Three databases (Medline, EMBASE, Scopus) were systematically searched. Resulting articles were exported to EndNote 20 software, where duplicates were removed. Strict inclusion/exclusion criteria were applied via two screening rounds where articles were discounted accordingly. Articles were assessed for bias using a critical appraisal framework specifically designed for laboratory-based research articles.

Of the 377 articles obtained, 11 were included in this review. Three concluded that JTV519 stabilised RyR2 through inducing calstabin2 binding to RyR2 (hence were calstabin2 dependent) whilst two concluded that JTV519's action was calstabin2 independent. Contrastingly, three concluded that JTV519 caused conformational stabilisation (termed

'zipping') of the 'domain switch' region of RyR2, thus stabilising RyR2, with two of these concluding that JTV519 interacted with subdomains which allosterically 'zipped' the 'domain switch'. Finally, three measured various arrhythmic parameters, concluding that JTV519 had multichannel effects aside~~s~~ from RyR2 regulation.

Evidently, Ca^{2+} regulation is fundamental to the action of JTV519 with RyR2 stabilisation a central mechanism of this. However, further research is required to determine the action of JTV519 on individual RyR2 mutations. Determination of the cryo-EM structure of RyR2 in different environments / with different mutations would facilitate this, enabling evaluation of each mechanism in different scenarios. In addition, further research is required to characterise multichannel effects of JTV519 in relation to CPVT.

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Complement-targeting therapeutics that are approved or in clinical development: A Rapid Review of the literature.

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Dysregulation of the complement system (CS) underlies many diseases; although this is extensively known, there has been a revival of interest regarding complement modulation in the face of the landmark approval of Eculizumab, a C5 inhibitor. This drug significantly improved clinical outcomes of many patients suffering from paroxysmal nocturnal haemoglobinuria and served as a clinical base for hypothetical concepts of the CS. Due to the rapidly evolving nature of the field, many new indications are now associated, and identifying causes and triggers for dysregulation and complement-mediated diseases proves challenging. However, advancements in disease molecules and increasing clinical experience, has aided in the recognition and understanding of the CS. We are now seeing an explosion of novel complement-targeted therapeutics, which aim to increase the indication for anticomplement drugs, and move beyond C5 inhibition. The aim of this search was to comment on the drug discovery landscape and assess targets, modalities, and strategies in improving efficacy for future therapy.[1]

PubMed and EMBASE databases were used in conducting a first search for reviews on anticomplement drugs in development or approved, to identify significant areas to focus on. Another main search was performed to identify research articles on current anticomplements.

65 papers were retrieved from the main search, which were then used in a table illustrating the anti-complement drugs.

Essentially, there are many promising candidates in the pipeline, targeting a several areas in the cascade, and coming in a diverse range of modalities. Increasing data from trials and clinical experience has shown there isn't a 'master inhibitor' approach; and other factors have come to surface, such as, infection risk, patient convenience and effective monitoring for individualised treatment. Nevertheless, improved medical advances and growing recognition of the pathophysiology of complement diseases will eventually lead to a wider range of therapeutics, which will support disease-tailored management.[2]

The Evidence to Support a Role for Inflammation in the Generation of L-DOPA-induced Dyskinesias: A Rapid Systematic Review

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Inflammation is known to play a central role in the pathology and progression of Parkinson's Disease (PD).[1] L-DOPA, the gold-standard, symptomatic treatment for PD is irreparably associated with L-DOPA-induced dyskinesia (LID), a debilitating experience for the patient. There has been a spike of interest as to whether inflammation plays a role in the generation of LID.[2] Therefore, this review aims to decipher whether the current data supports a role for inflammation in LID generation.

The search algorithm was defined and run through several databases. Studies in accordance with the inclusion criteria were included, all studies were critically appraised using SYRCLE's risk of bias tool.[3] Bibliographies of relevant literature were screened for proteomic and genomic research to assess whether their findings supported those found by included papers.

Most research was carried out in 6-hydroxydopamine (6-OHDA) Sprague-Dawley rats, activated microglia (OX-42) was the most measured inflammatory marker. 60% of papers concluded evidence for a role of inflammation in dyskinetic animals receiving L-DOPA compared to control groups. Neuroinflammation was only observed in the 6-OHDA model when there was a short post-L-DOPA interval or a long post-lesion interval. Genomic and proteomic studies revealed many factors could be involved in the etiopathogenesis of LID, not providing evidence for a role of inflammation.

Models failed to reproduce the pathological hallmark alpha-synuclein (α-synuclein) and dopamine denervation occurred too rapidly, resulting in poor clinical translatability.[4] Consequently, animal models symbolise models of dopamine loss, not PD. Researchers failed to include perfect control groups, therefore cannot be certain inflammation is the only underlying mechanism of LID. Genomic and proteomic papers raised concern of negative reporting amid the literature.

This review concludes current evidence for a role of inflammation in LID generation suggests inflammation is not a key driver, although many models demonstrated increased neuroinflammation the source of inflammation remains inconclusive.

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The management of depression in Alzheimer's Disease in the community - A rapid review evaluating pharmacological and non-pharmacological modalities of treatment.

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Alzheimer's Disease (AD) is the most common form of dementia, accounting for 62% of diagnosed dementia patients in the UK.[1] Depression in dementia can be seen in up to 50% of AD patients.[2] Treatment for depression in AD is mainly seen as a pharmacological issue, with antidepressants at the forefront to try and reduce depression levels in AD patients in the community. Previous reviews, evaluating efficacy for antidepressants in dementia have found that there is not strong enough evidence to support the use of antidepressants. This rapid review aims to evaluate pharmacological and non-pharmacological means of treating depression in AD patients in the community, by gathering and analysing relevant literature. This study hypothesized that numerous treatments are used throughout the community, with minimal efficacies supporting them.

Four databases were screened for relevant literature. Studies found via database searching were screened for duplicates and screened against eligibility criteria to focus on the aim of this review. Critical appraisal tools were used to assess the quality and level of bias of each included paper. Studies were then discussed qualitatively. This rapid review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[4]

Ten studies were included in this rapid review. Studies included covered pharmacological and non-pharmacological treatments of depression in AD. The studies ranged in design, covered the years 2009-2021 and were based worldwide.

After evaluation of the literature, the review found that antidepressant treatment was not found to be superior to placebo treatment and that antidepressants are widely prescribed in AD cohorts despite the lack of efficacy, suggesting prescribing habits and education need to be adjusted. Non-pharmacological treatments are a promising avenue for the treatment of depression in AD, but further higher quality trials are needed to support the use of the non-pharmacological interventions discussed.

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Development and validation of a standardised ELISA for detection of complement factor H in plasma for the use in psychosis

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Psychosis is a debilitating mental health disorder, occurring in a range of mental health diseases such as schizophrenia, causing the individual to "break away from reality" and experience the world around us in a much different way.[1] With suspected involvement of the immune system, in particular the blood-based complement system in the development of psychosis, recent research has identified an upregulation of complement regulator factor H (FH) via proteomics in clinically high-risk individuals (CHR), years prior to their first psychotic episode.[2] FH is a regulatory protein in the alternative pathway that prevents the overactivation of the complement system.[3] Yet, commercially available FH enzyme linked immunosorbent assays (ELISA) cannot validate the proteomics findings. There is a current need to produce optimised clinically viable assays that can quantify FH accurately in aid for early prognosis of psychosis.

We developed, optimised, and standardised an indirect sandwich ELISA that can capture FH at its short consensus repeat (SCR)10-15 domains where it does not interfere with its regulatory and co-factor abilities. Each step within the ELISA was optimised through a comparison of different concentrations for optimal signal-to-noise ratio.

Our optimised ELISA was comparable with commercially available assays, with wide range of detection, moderate sensitivity, and an intra- and inter- co-efficient variation (C.V.%) of <10% and <15% respectively.

Further optimisation of assay is required to improve sensitivity, increase accuracy of FH quantification within normal plasma, and improve precision via further reduction of C.V.%. Validation of the FH ELISA will be conducted in a CHR and control cohort. A completely optimised assay, along with psychiatric assessments, can increase the identification of CHR individuals and allow an implementation of early treatment.

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The Role of Dietary Polyphenols in Inhibiting Pathogenic Microorganisms – A Rapid Review

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Polyphenols are natural substances found in fruits, vegetables, and beverages.[1] They are widely known for their health benefits such as reducing the risk of cardiovascular diseases, diabetes, cancer, and bacterial infections.[1] Polyphenols limit free radicals by binding to ROS and increasing basal levels of antioxidant enzymes.[1] Since antibiotic resistance is a major problem worldwide; many researchers are keen to explore cheaper natural alternatives to antibiotics such as dietary polyphenols which have less undesirable side effects.[2] This project aims to investigate the role of dietary polyphenols in inhibiting pathogenic microorganisms.

A literature search of Scopus, Medline, Web of Science, EMBASE, and Cochrane Library was conducted in October 2021 using a refined list of search terms. Articles were imported to EndNote and screened against an inclusion and exclusion criteria. Papers were critically appraised using CASP and laboratory experimental-based research critical appraisal tool to assess the quality and risk of bias of included studies.

Out of 1661 results, 16 final papers were selected for the review. Some studies were excluded due to their irrelevance to polyphenols' role in inhibiting pathogenic microorganisms.

Polyphenolic compounds found in foods inhibit the growth of gram-negative, gram-positive, MRSA and coronavirus *in vitro* and *in vivo*[1] Moreover, polyphenols have a positive effect on the gut by increasing the concentration of the healthy microorganisms while decreasing the levels of potentially pathogenic species.

Studies assessed in this review have limitations, mainly because different methods were used which limited our capacity to compare the results. Therefore, a standardised method should be applied for further studies to gain consistent and generalised results.

This review found that different dietary polyphenols inhibit the growth of pathogenic bacteria *in vivo* and *in vitro.* The findings of this review have implications for researchers to discover natural safe alternative to antibiotics to inhibit pathogenic microorganisms and help reduce antibiotic resistance crisis.

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Are Beta-blockers effective in the treatment of Takotsubo Syndrome? A rapid review of the literature.

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Takotsubo syndrome (TTS) is an acute cardiomyopathy characterised by left ventricular systolic dysfunction without any obstructive coronary artery disease.[1] It is a relatively rare disease, but the number of cases have been increasing over the last 20 years. There is no licenced drug that exhibits effective protection against mortality or recurrent episodes in TTS but a multitude of drugs, including beta-blockers are indicated.[2] Beta-blockers have shown a positive effect in treating other cardiomyopathies and are suggested to have a similar effect in TTS. The aim of this project is to determine whether beta-blockers are effective in treating TTS and if further studies are necessary.

The three online databases of Scopus, Embase and Medline were consulted to identify literature evidence on the use of beta-blockers in the treatment of TTS. A search algorithm was created and replicated on all databases using the keywords 'Takotsubo syndrome' and 'beta-blockers'. The resulting papers were screened for relevancy based on the inclusion/exclusion criteria. After being critically appraised a rapid review of the literature was conducted.

Results showed that beta-blockers have a positive effect in treating left ventricular dysfunction and related complications of the initial event. However, they show little to no effect as a long-term preventative measure of recurrent episodes of TTS.

The data within this rapid review suggest that beta-blockers may be a viable treatment for the initial TTS event rather than as a preventative measure and propose that more research must be done to support this. As the majority of the patients were female, the role of sex may play a factor in the prevention and pathogenesis of

the disease and needs to be investigated. There are no randomised control trials done to investigate the of beta-blockers in TTS and these are critical to provide significant data that may influence therapy.

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Cell Transplantation Therapy in Parkinson's Disease – Why Cells Die Post-Transplantation into the Brain: A Systematic Rapid Review

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Parkinson's disease is characterised by the degradation of dopaminergic neurons in the substantia nigra, resulting in movement disorders.[1] Whilst symptomatic treatments are available, there are currently no effective therapies promoting recovery or repair after cell loss.[2] As such, cell transplantation therapy is undergoing investigations as a potential therapeutic intervention.[3] However, poor graft survival has proven to be a hindrance in the therapy's success.[3] Hence, to improve therapeutic outcome, we must identify and understand factors that affect cell survival post-transplantation.

A systematic rapid review was conducted to analyse relevant pre-clinical studies that quantitively assess cell survival post-transplantation, to determine why graft survival is limited and possible interventions to promote survival. Three databases; Scopus, PubMed, and Web of Science, were searched to identify relevant research to answer the review question. All articles were screened against eligibility criteria to determine suitability for inclusion. Data collected included: disease model, animal model, cell type, transplantation area and outcome data. Where data was not presented as percentage of cell survival, secondary objectives such as histological and immunostaining analyses were used to draw a conclusion. Results were analysed topically through a narrative synthesis to answer the review question.

20 pre-clinical studies met the eligibility criteria fully. The main findings were an active host immune response, the presence of specific genes within donor cells, along with integrity and age of donor cells, reduce graft survival. Promising interventions to enhance survival include stimulation of the substantia nigra or transplanting cells within specific biomaterial that releases a specific neurotrophic factor in a prolonged manner.

Although the evidence indicates multiple factors impact graft survival, specific conclusions regarding precise mechanisms of cell death remain unclear. It would be desirable for future studies to examine grafts at multiple time points over extended durations to observe its fate, through conducting bioluminescence analyses.

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An investigation into the carbon footprint of pharmaceuticals: a rapid review of a current literature

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Climate change has been a considerable challenge in the past few decades, the release of greenhouse gas emissions, particularly carbon dioxide.[1] Medicines and pharmaceutical products account for 20% of the emissions in NHS England.[2] Until the past few decades, the environmental impact of the pharmaceutical industry was not seen as a significant issue.[3] The health and pharmaceutical industry have a moral responsibility to decarbonise its practices and reduce their pollution contribution to prevent the exacerbation of climate change-related disease . This study aims to depict the current status of studies into sustainability approaches to pharmaceutical carbon footprint, identify research gaps, and suggest new areas to research.

Medline, Embase, Scopus and Web of Science were the chosen databases. The analytical data will be extracted through qualitative thematic analysis. This rapid review will follow extract data systematically by collecting descriptive data of specific characteristics from the selected studies. The thematic analysis identifies recurrent concepts and themes formed through a systematic text condensation technique used in data synthesis.

The literature search yielded 1739 papers, 30 articles were selected. The thematic analysis had identified six concepts and three themes; the optimisation of pharmaceutical consumption in Healthcare, sustainable manufacturing of Pharmaceuticals and sustainability assessments relevant to the pharmaceuticals carbon footprint.

Addressed the concepts and themes identified key barriers were; Lack of financial incentives for change, Limited access to primary LCA data; Lack of a standardised method of sustainability assessments that most stakeholders/sectors find accessible or useful, lack of responsibility for resource consumption across sectors. Key facilitators were; opportunities for a carbon tax instilled place; establishing an objective third party to keep standards across sectors, and the development of mutual standards for pharmaceutical life cycle analysis.

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The risk of antibiotics in the aquatic environment: a rapid systematic literature review

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Antimicrobial resistance results in the death of 33,000 people every year in the European Union.[1] An emerging cause of antimicrobial resistance is the environmental presence of antibiotics contaminating the natural environment, particularly our waterways.[2] Potential aquatic toxicity is unknown as many of the antibiotics were licensed before an environmental risk assessment was a part of the European medicines agency appraisal process and with antibiotic consumption rising it is imperative to monitor the risk they pose.[3]

The aim of this project is to determine which antibiotics pose the most significant threat to the European aquatic environment and compare the risk between different regions.

The search was conducted using four databases; Emcare, Medline, Web of Science and Global health; these were screened to find titles relating to the risks of antibiotics in the aquatic environment and were selected following the inclusion and exclusion criteria. Papers were chosen only if published in the last ten years to ensure the results were as up to date as possible. These publications were then critically appraised using a checklist developed for laboratory-based research.

21 studies met the search criteria, which was cut down from the original 823 publications that had first been identified. Narrative analysis was used instead of a meta-analysis due to the lack of standardised approaches towards data acquisition and analysis in the papers. The papers were from 12 different European countries, with Spain being the most reported region. The antibiotics of most concern to aquatic ecosystems were amoxicillin, ciprofloxacin, azithromycin, and piperacillin (reported risk quotient > 10). The antibiotics ciprofloxacin, metronidazole, sulfamethoxazole, and trimethoprim were found in the highest concentrations across the publications (> 500ng/L) and 79% of the antibiotics reported had an RQ value of above 1 (moderate

threat to marine life). However, due to the differences in sampling methods and sample sizes of the publications, the results cannot be certain.

This review has highlighted the need to improve the environmental risk assessment to be more specific to antibiotics. Findings support that certain measures need to be implemented to mitigate the input of antibiotics into the environment and that the environmental risk assessment should be conducted on pharmaceuticals that were licensed before 2006. The variation in results from country to country is significant, and therefore provides a rationale for regular sampling. More research needs to be conducted in this area, not just for antibiotics but other classes of pharmaceuticals, so problematic compounds can be identified, and strategies to combat the risk can be developed.

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A Rapid Review into the Testing Methods of Trace Elements with the Intention of Application to Parenteral Nutrition

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Parenteral nutrition (PN) is a crucial part of certain patients' care.[1] One of the components of PN are the trace elements (TEs). Consisting of nine elements in total, these required nutrients play critical roles in body function.[2] This study aimed to theorise a potential method for TE analysis in PN to ensure patients are receiving the correct dose. The studied aimed to answer the research question 'How can current analysis methods of trace elements be employed to test trace elements in PN?'

This study employed rapid review methodology to analyse data from publish articles. Three databases were searched for related papers: Web of Science, PubMed and Scopus. The search terms used for the initial search were 'analysis', 'trace element', and 'stability'. Articles published before 01/01/1990 and any non-English language papers were excluded from the review.

Eleven of the sixteen included studies analysed TE concentrations using Inductively coupled plasma mass spectroscopy (ICP-MS). Six of the sixteen articles used atomic absorption spectroscopy (AAS) to quantify TE within samples. Other techniques observed include total inductively coupled plasma optical emission spectroscopy, present in three studies and total reflection x-ray fluorescence, HPLC and ion chromatography, found in only one study each. The overall quality of the included articles was moderate.

The review concluded that the most prevalent and feasible method for TE analysis in PN would be ICP-MS. It was observed that use of AAS would require different instrumentation for each element which would decrease its efficiency and usefulness. It was also suggested that there may be many barriers present to the clinical feasibility of TE testing via ICP-MS or any other method. This includes factors such as cost, availability of testing apparatus and possible increased NHS workload. However, a new method could revolutionise clinical practice and actually remove pressure on NHS staff and resources.

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Exploration of on-site testing methods for psychoactive drug identification and quantification, from the perspective of the amphetamine type stimulants

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The number of drug-related deaths from use of the new psychoactive substances has increased by 137% in England and Wales from 1995 to 2020.[1] The illegal production of these psychoactive drugs is not regulated at all. Recreational drug users cannot rely on the identity, purity, or dosage of purchased substances. Two people taking the same nominal drug substance could have random, potentially fatal outcomes.[2] The need for drug testing is for the purposes of harm reduction. To provide the most effective harm reduction service, rapid in-field testing of drugs at sites such as festivals is required. A drug group of popularity at these in-field sites are the amphetamine-type stimulants. They are a group of close structural analogues, that therefore represent an analytical challenge.

Drug analysis technologies were explored to provide recommendations for in-field drug testing of powders and tablets. Aspects such as costs, throughput, portability for on-site use, and scientific reliability were evaluated. A rapid review of relevant high-quality peer-reviewed literature was undertaken. The databases searched included: Medline, Embase, Scopus and Web of Science.

Thirteen papers were included based on their eligibility criteria: Four papers looking at various applications of Mass spectrometry; Four looking at Infrared spectroscopy; Three papers looking at various colorimetric test applications; Single papers looked at Raman spectroscopy and Ultraviolet (UV) spectroscopy respectively.

Aside from the UV spectroscopy technique, all the approaches identified in this rapid review have shown potential to be recommended for in-field use. Naturally, each analytical technique had positives and negatives. Ultimately recommendations for analytical techniques vary greatly upon each particular harm reduction setup – considering factors such as the demand for their services and their budget. Many of the papers identified were novel, newly developed approaches which require further testing using larger sample numbers to obtain more reliable data on their validity.

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The evidence to support a role for inflammation in the generation of L-DOPA induced dyskinesia

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Levodopa induced dyskinesias (LIDs) are a problematic complication in long-term treatment of Parkinson's disease. It is a motor fluctuation that occurs in up to 80% of PD patients after long-term L-dopa treatment, with the percentage of affected patients increasing over time.[1] Treatment of LID requires careful clinical examination to find the type of dyskinesia as different approach is required for different types.[2] It is also not well understood by medical professionals and researchers are still looking for an approach to treat and prevent LIDs through various methods. The main element of PD pathogenesis that we are focusing on this review is on the inflammation in LIDs.

There have been limited amount of evidence from research papers and reviews as to what exactly caused LIDs, hence along with different research methods and techniques, we are taking a look at papers to explore the evidence to support a role for inflammation in the generation of LIDs.

After comparing the papers found in the literature databases, all but one paper used methods for dopamine deficit in order to create PD rat models. The studies were summarised and the data collected was reviewed to conclude an overall discussion as to how inflammation is causing LIDs. Factors were taken into consideration to understand the severity and inconsistency of abnormal involuntary movements (AIMs), like the stage of illness, dosage of L-dopa, frequency of L-dopa treatment and the youth of the patient at the onset of symptoms.

In this review, it is required to analyse these findings from the papers in order to provide evidence to support the development of LIDs in the rats that are associated with the activation of different inflammatory markers promoting inflammatory responses, from cell structures like astrocytes, microglia and cytokines.

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Evaluation of the ASSIST-CKD Kidney Function Graph Surveillance Programme for the Early Identification and Treatment of Patients with Progressive Chronic Kidney Disease

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Chronic Kidney Disease (CKD) is a long-term condition where there is a gradual loss of kidney function that affects around 10% of the UK population[1]. It is often detected too late in the end stages of CKD where there are few treatment options that affect patient quality of life. ASSIST-CKD is a clinical service that monitors the patient's renal function who are at greatest risk of developing CKD, they notify the general practitioner sooner in comparison to if the system was not used[2]. This project evaluates the benefits of using the ASSIST-CKD in Southwest Wales on a patient individual scale.

Data was evaluated from two patient databases: Vital Data and ASSIST-CKD between November 2017 and June 2021 at Morriston Hospital Renal Unit, Swansea. Data was inputted and anonymised then manipulated in Excel. A total cohort of 1,021 patients were included, 748 of these were included in a sub-cohort analysis.

Late presentation rates to renal services had increased from 9.7% in 2019 to 17.1%[3]. Using ASSIST-CKD, patients average renal function per year increased in all indicative stages of CKD. Planned haemodialysis rate was 50%, which did not meet the UK Renal Registry target of 60% of planned haemodialysis patients to receive an arteriovenous fistula or arteriovenous graft at first haemodialysis treatment[4].

There are some benefits of using ASSIST-CKD as it indicates responsibility of the increase of average renal function difference per year and supported patients earlier than intended. However, the Coronavirus pandemic may have contributed largely to late presentation rates and inability to meet the Renal Association planned haemodialysis target. Further development of these findings needs to be carried out over a longer time period on a larger scale to follow the full patient journey instead of a snapshot of time.

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Do PCSK9 inhibitors have a beneficial effect in diabetic patients and go beyond LDL-cholesterol management in those with hyperlipidaemia? A rapid review

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Despite present steps in type 2 diabetes mellitus (T2DM) therapies, mortality and morbidity remains high.[1] Cardiovascular death is the most common cause of death in these patients.

Cardiovascular outcome trials showed that some proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) proved to be effective at reducing cardiovascular death, and in particular, reduce low-density lipoprotein cholesterol (LDL-C) levels in patients with hyperlipidaemia.[2] This encouraged research into the use of PCSK9is in patients with T2DM, to reciprocate these outcomes in addition to determine if this inhibitor would reduce other glycaemic parameters. The aim of this study is to determine whether PCSK9is are beneficial in T2DM patients, regardless of hyperlipaemia status.

This review was managed in accordance with the Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. An electronic literature search was conducted using the databases PubMed, Scopus, Medline and Embase. The review concentrated on randomised controlled trials (RCTs) and their relevant subgroup analyses. The Cochrane tool for assessing the risk of bias and CASP checklist for quality assessment of the papers was used to critically appraise the selected studies.

Results observed eight RCTs, with the two largest RCTs for these inhibitors included in the review. All eight RCTs were considered to be at low risk of bias and of high quality. Results from these studies showed that PCSK9is had a beneficial effect in lowering a composite of cardiovascular death (HR 0.85; 95% CI 0.79-0.92; P<0.001)[3] and an almost 60% reduction in LDL-C levels, however no change was observed in haemoglobin subunit alpha 1 (HbA_1) and fasting plasma glucose (FPG) in the T2DM population.

PCSK9is were associated with a reduction in a few clinically important T2DM related outcomes, however these benefits were observed in all patients regardless of diabetic status. The findings suggest that the decision to prescribe PCSK9is in T2DM and the need for these agents to be included into T2DM guidelines is not certain. The exact mechanism by which PCSK9is exert these glycaemic effects stays undetermined, and further studies are required to explain this.

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Evaluation of the proposed mechanisms of action of dantrolene in the treatment of RyR2 dysfunction in genetic and acquired ventricular arrhythmia - A Rapid Review

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The cardiac ryanodine receptor (RyR2) is essential to several Ca^{2+} activated cellular processes, facilitating Ca^{2+} release from the sarcoplasmic reticulum.[1] In arrhythmogenic cardiac disease, these processes become dysregulated, and this is thought to be due to defects in the functioning of RyR2.[1] Current therapies lack specificity and are not fully protective for patients, which has led to the search for novel pharmacological agents that target RyR2. Dantrolene (a licensed skeletal muscle relaxant) has been identified as a compound that may attenuate this RyR2 channelopathy,[2,3] however the mechanism by which this is likely to occur remains unclear. This review aims to evaluate proposed mechanisms of action of dantrolene in the treatment of arrhythmia related RyR2 dysfunction.

A search of the literature was conducted using Medline, EMBASE and Scopus, combining a series of search terms relating to ~~either~~ “ventricular arrhythmia”, “RyR2” or “Dantrolene”. Publications identified were then screened for eligibility using set inclusion and exclusion criteria and the remaining articles were then quality assessed. Data was then extracted from those papers deemed suitable to identify mechanistic information.

The literature search produced 198 results, of which 12 were deemed suitable for inclusion. Dantrolene was found to exert several different actions on dysfunctional RyR2 via direct binding, to inhibit abnormal Ca^{2+} release. These mechanisms largely involve modulating intra-molecular interactions within the channel, as well as interactions between the channel and the regulatory binding protein calmodulin to induce changes in channel gating.

This rapid review summarises the existing literature on the proposed mechanisms of action of dantrolene in the prevention of ventricular arrhythmia associated with RyR2 dysfunction, however further research is required to fully elucidate these mechanistic effects, especially with respect to the role that other RyR2 accessory proteins may play in mediating the effects of the compound.

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Molecules derived from *Taraxacum officinale* with antibacterial and antiviral activity, a rapid review.

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Plants have been used for their medical properties since the olden ages, with herbal remedies still a common alternative medicine to pharmaceutical therapies. A certain species knows as *Taraxacum. Officinale* has demonstrated a wide spectrum of antibacterial and antiviral activities, as new diseases emerge and antibiotic resistance increases on a global scale, the necessity of finding new medicines capable of tacking these superbugs is paramount. This rapid review aims to collate recent research and identify the molecules within the plant with potential for future drug development.

Four databases were explored; Embase by Ovid, Medline by Ovid, Web of Science and Cochrane Library to find antibiotic and antiviral activities within T. *Officinale*, both *in vitro* and *in silico.* A total of 14 studies were included in the review after being screened through eligibility and exclusion criteria, and later assessed for their bias and quality.

This review was able to encapsulate the wide range of molecules and extracts identified in their contribution for T. *Officinale* activity, summarizing their method of action and potential for drug development

Molecules and extracts derived from *T. officinale* exhibited broad-spectrum antibacterial activity, but affected gram-positive bacteria. Some antibacterial molecules identified include 4 novel flower peptides, phytol and luteolin. Anti-viral compounds include cichorrin and luteolin.

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Exploring inhaler prescribing across NHS Wales Primary Care and its impact on the environment.

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Inhalers are important for the management of respiratory diseases such as asthma and COPD. However, these devices contain powerful greenhouse gases and contribute to global warming from their manufacturing and use.[1] In April 2019 Wales was the first country to declare a climate emergency.[2] As a result, official organisations such as NHS Wales, NICE and BTS introduced guidance changes in the prescribing of inhalers to reduce inhaler carbon emissions, focusing on the prioritisation of lower carbon footprint inhalers over higher carbon footprint inhalers.[3] Since these guidance changes, inhaler prescribing in Wales has not been investigated.

This project consists of analysing inhaler prescribing data with inhaler carbon footprint data, alongside recent changes in inhaler prescribing guidance. The results produced were used to understand to what extent Wales has adhered to changes targeting the reduction of carbon footprint levels through inhaler prescribing.

The main reduction in carbon footprint seen over time is largely due to the overall decrease in the total number of inhalers prescribed. This is primarily explained by the prioritisation of combination inhalers over single active inhalers, rather than through the implementation of switching higher carbon footprint inhalers to lower carbon footprint inhalers as suggested through prescribing guidance changes, which was not evident.

Many of the goals set to reduce carbon footprint levels through inhaler prescribing are achievable. However, there is a lack of bridging between guidance and physically implementing these changes throughout NHS Wales. With support, the goals set could be reached through the development of the roles of healthcare professionals, such as pharmacists, in truly implementing these changes within Wales to uphold greener inhaler use.

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Why do cells die post transplantation into the brain? A systematic-rapid review of the pre-clinical data.

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Stem cells are widely used in preclinical models to investigate their potential for repairing brain damage associated with neurodegenerative disease.[1] Research is promising in terms of attempts to improve neurological dysfunction however, most cells die post transplantation.[2]

The aims of this systematic-rapid review were to assess the pre-clinical data of interventions made by researchers to improve cell survival and to develop a greater understanding of their cause of death. Literature search was conducted in databases PubMed, Scopus, and Web of Science. Articles extracted from the search were initially reviewed by four individuals against an eligibility criterion, literature focused to the research aims were included.

A qualitative analysis of 18 included studies identified eight different approaches that researchers have undertaken to improve cell survival post-transplantation. The greatest amount of cell death occurred within the first week post transplantation; this was comparable between included studies. Efficacy of long-term survival was greatest in studies which collected data for extended time periods. Inconsistent timescales analysed between included studies reduced comparability of results. Phenotypic identification of new neurons, proliferation, microglial and astrocyte cells supported the efficacy of results in determining cell survival and cause of death.[3]

In conclusion, cell survival is poor, and the cause of death is multifactorial. A consistent observation of host rejection within the literature identified a need for further research to be undertaken to overcome such hurdles to obtain long term survival.[4]

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Investigating the use of drug repurposing for the development of novel and safe drugs in oncology: a rapid review of the literature

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The cancer survival rates today are relentlessly low, and further strategies are urgently required to tackle the global cancer burden.[1,2] Drug repurposing is an alternative strategy that could potentially help to increase the output of novel anticancer therapies. Repurposing identifies and exploits new therapeutic uses from existing drugs, outside their original indication, accelerating the conventional development timeline while reducing the costs and risks of failure associated.[3] This review aims to examine the field of drug repurposing in oncology, particularly the barriers as to why repurposing has yet to become a mainstream strategy within the pharmaceutical industry.

Advanced searches were conducted on EMBASE, MEDLINE, Scopus, and ClinicalTrials.gov databases to identify relevant literature on repurposed drugs that have progressed to the cancer clinic. The articles were

assessed against a pre-set eligibility criteria and a PRISMA flow diagram was utilised throughout. Relevant data was extracted from each study and the risk of bias of each study was assessed using Cochrane's risk-of-bias tool.

Ten studies were included in the final review, all of which were randomised controlled trials within phase III of clinical studies. Most of the studies demonstrated improvements in the primary endpoints assessed, with some exhibiting no significant differences but did not result in increased toxicity. The adverse events observed were minor except for the thalidomide trials, which demonstrated high incidence rates of grade 3&4 adverse events.

The results demonstrated evidence for drug repurposing as an effective strategy to develop novel and safe anticancer therapies. There is still a significant deficit of repurposing trials within the industry primarily due to the intellectual property and regulatory barriers. Repurposing has the potential to have a large role in the future of oncology, but measures need to be implemented to increase the funding and incentive for repurposing initiatives.

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Investigation into the clinical features and deaths of TCA-related overdoses in England and Wales from 2015-2020.

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The narrow therapeutic window and extensive toxicities of tricyclic antidepressants creates an ongoing issue in regards to intentional and unintentional overdoses. This project is an extension of the previously conducted study involving single agent TCA-related overdoses, now looking at the impact of polypharmacy specifically. This danger of toxicity therefore forms the basis of this project with its aim to investigate the clinical features and mortality of TCA-related polypharmacy overdoses. Prescribing data, mortality data and lastly data regarding overdose was collected from All Wales Therapeutics and toxicology centre (AWTTC) for the years 2015-2020 across both England and Wales.

The results found increases in prescribing of amitriptyline and nortriptyline across both the primary and secondary care sectors in England and Wales, whilst all other TCA prescribing rates have decreased over the same time period. The United Kingdom Poisons Information Database showed a prevalence of neurological features present in enquiries with a severity score of minor, moderate and severe. However, with enquiries categorised as fatal and resulted in patient death, renal/biochemical clinical features had the highest occurrence. The Office of National Statistics provided data regarding TCA related deaths and showed a decrease in TCA-related deaths over these six years.

The decrease in prescribing of all TCAs aside from amitriptyline and nortriptyline may be accounted for by their removal from the first line as a treatment for depression. Amitriptlyine and nortitpyline are commonly use in treating other conditions such as neuropathic pain and insomnia so their increase in use is accounted for and understood.[1]

To conclude, TCA-related polypharmacy overdose leads to greater rates of fatalities and increased severity of clinical features. With this in mind, greater monitoring and caution of TCA prescribing is crucial to ensure patient safety.

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Evaluating Health Inequalities in the Primary Care Prescribing of Anticoagulants within Wales from January 2016 to August 2021

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National Institute of Health and Care Excellence (NICE) provide guidelines on the treatment of conditions to prevent treatment differentiation between areas in the UK. Postcode lottery is where there are Health inequalities due to geographical location.[3] In 2019, 78,905 patients in Wales have a diagnosis of Atrial Fibrillation (AF). Those that are at risk of clotting due to being diagnosed with AF and CHA2DS2-VASc of two or more, are prescribed anticoagulants.[1] The aim of this study was to identify and investigate health inequalities in the primary care anticoagulant prescribing in the 64 GP clusters within Wales.

Comparative Analysis System for Prescribing Audit (CASPA) database was used to obtain Welsh primary care prescribing data from January 2016 until August 2021. Data on vitamin K antagonists, antiplatelets and direct-acting oral anticoagulants (DOACs) were obtained.

Antiplatelets were the most prescribed across all primary care clusters over the years. However, aspirin is commonly used in conjunction with an anticoagulant therapy. The prescribing of vitamin K antagonists has been slowly decreasing since January 2017, Betsi Cadwaldr in particular showed a significant decrease. Since January 2016, a shift towards prescribing of DOACs can be seen furthermore, COVID-19 has further improved the rise in prescribing levels.

Due to DOACs requiring little monitoring than warfarin they were favoured during COVID-19. NICE guidelines recommend DOACs as first-line treatment.[2] Time taken to travel to GP impacts patients chances to have medication reviews this was shown by Powys which had the longest travel time by public transport to a GP surgery and has the lowest prescribing of anticoagulants.

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Exploring the views of healthcare professionals on the feasibility of implementing an antibiotic allergy delabelling service in primary care

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About 10% of the UK population have a recorded penicillin allergy, but it's estimated that over 90% of these labels can be excluded following comprehensive testing through the antibiotic allergy delabelling service.[1] Current allergy delabelling services take place in secondary care.[2] Limited research into the topic means there's a need to explore the views of healthcare professionals (HCPs) to understand whether it could be implemented into primary care and discover what factors may positively/adversely affect its success.

Due to the exploratory nature of this study a qualitative approach was adopted. Following ethics approval, semi-structured interviews were conducted with a range of occupations within the primary care setting. Interviews were recorded, transcribed and coded via thematic analysis to identify common themes using both deductive and inductive approaches.[3]

There was limited knowledge across the interviews on what delabelling was and the extent of the issues with allergy labelling records. Many barriers were identified along with several enablers to overcome potential challenges surrounding implementation of the service such as resources and linking of different primary care settings. Participants raised differing proactive and reactive approaches for the recruitment of patients into the potential service. Different methods of delabelling were discussed and structured history taking was the most widely accepted method.

Lack of knowledge surrounding issues with antibiotic allergies in primary care suggest that staff and patient education is essential to raise awareness on the potential of antibiotic allergy delabelling. Their opinions suggested that while it is plausible for the service to take place in primary care, there are several barriers and enablers that need to be addressed to make it successful. For future research, responses from a survey targeted to a wider audience of HCPs should give more valuable insights into whether the service could be implemented and how it would be carried out.

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Exploring how pharmacist independent prescribers change their scope of practice and their views on the potential new role of a Designated Prescribing Practitioner.

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Pharmacist independent prescribers (IPs) came into practice in 2006 following the second crown report (1999).[1] Pharmacists are now licensed to prescribe medication for any clinical condition within their competence but excluding 3 controlled drugs that are prescribed for addiction.[2] The pharmacist when studying to become an IP will agree on a specific area of expertise with the university, within which to practice. The competent IP will only prescribe within this scope of practice (SoP). If an IP subsequently desires or needs to widen their SOP, this may be achieved by either expanding or changing their SoP. The Royal Pharmaceutical Society (RPS) now allows 'Designated Prescribing Practitioners' (DPP) to supervise the 90 hours of practical work instead of a Designated Medical Practitioner (DMP or DSMP).[3]

As this study revolved around IPs who currently practice in Wales quantitative research was the chosen method as the geographical area that needed to be covered was large. A questionnaire was devised via Microsoft Forms and published on the social media of HEIW and later retweeted by the RPS. A reminder post was published the data was then descriptively analysed via excel.

The study revealed there has been a gradual increase in the number of pharmacists who are becoming IPs. Of the 59 respondents, 80% expanded their SoP and 61% changed their SOP. The IPs identified a lack of clear structure and support as the main barrier when expanding/ changing their SoP. When questioned about the new role of the DPP respondents emphasised their lack of confidence in their clinical and diagnostic skills which undermines their confidence in undertaking this role.

This paper identifies the need for a framework to demonstrate the ongoing competence of an IP including when expanding/ changing SoP. This study also highlights the educational needs of becoming a DPP that need to be addressed.

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Evaluating the Ambulatory Chemotherapy Service at UHW to Suggest Improvements to Ambulatory Chemotherapy Services in General

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Ambulatory chemotherapy allows patients to receive their treatment at home using a CADD (computerised ambulatory delivery device) pump in a specially designed backpack.[1,2] Patients only have to go into hospital for short periods of time for daily blood tests and monitoring. This study aimed to make suggestions for service

improvement to the ambulatory chemotherapy service provided to blood cancer patients at University Hospital of Wales (UHW) through analysing responses to patient and carer questionnaires.

Two questionnaires were conducted by staff at UHW; one for patients who were not using the service to assess the need to restart the service after it was stopped during COVID-19 restrictions, and the other was for carers of patients who had used the service asking for their opinions. Quantitative data was analysed by forming graphs and qualitative data was analysed using conceptual content analysis and divided into themes and sub-themes.

50% (n=3) of patients said they would prefer treatment at home and 50% (n=3) said they would prefer to receive treatment in hospital. Carers spoke highly of the service but suggested improvements to the day care unit such as a coffee machine and providing a parking pass. Carers felt well supported and 12/17 carers (71%) strongly agreed that they would support their relative/friend having treatment in ambulatory care again.

Recommendations included making a leaflet specifically for carers and continuing to gather and analyse patient and carer feedback on a much larger scale. Overall, patients prefer the comfort of being in their own homes but having to go into hospital every day is a burden for both patients and carers. Further work should include conducting more extensive questionnaires, using video calls to visually assess patients and research into blood tests that patients could do themselves at home.

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The Patient Perspective on Neurosurgical Clinical Trials- How and When Is It Captured? A Systematic Review

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The advancements within clinical research of Parkinson's Disease (PD) have resulted in far more invasive forms of intervention. Researchers are moving more towards the direction of neurosurgery with hopes of slowing disease progression and possibly reversing degeneration of the disease.[1-3] As clinical trials become more advanced in their interventions, higher expectations of participants are required through more vigorous testing.[1] It is therefore important to value the perspective of the patient participating in invasive trials. This systematic review aims to look at how, when and what is captured surrounding the experience of the participant when entering such trials.

Five databases were screened: MEDLINE, Embase, PubMed, Scopus and Web of Science where a total of 10 studies were included based on the inclusion/exclusion criteria. Data was extracted from the included studies and quality assessed. Data was further extracted from two pilot interviews of previous participants of the GDNF trial and the 2021 NECTAR conference in Edinburgh before being compared to the results of the included studies.

This review found limited data surrounding participant perspective throughout clinical studies with a vast majority recording experience retrospectively. Many papers explored the informed consent process and the importance of enhanced patient-researcher relationships. Data from both the included studies and wider resources aided recommendations for future trial protocols to include participant perspective in the trial design.

Recommendations for future trials included the following: enhanced staff training, addition of aftercare procedures after trial cessation, psychological support for participants and family/carers and expanding participant involvement within the trial design. Further investigations into the participant experience are sought to understand the impact that participant experience can have on both the individual and the trial itself.

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Why do cells die post-transplantation to the brain? A rapid systematic review

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For many years, cell transplantation therapy has been extensively studied by scientists as a treatment for neurological disorders such as Parkinson's disease, Alzheimer's disease, and Huntington's disease.[1] Recent research has shown that poor therapeutic outcomes of cell transplantation therapy are caused by poor survival of grafted cells, which limits the further development of cell transplantation therapy.[1] This literature review aims to provide researchers with a better understanding of some of the reasons why cells die after transplantation, so that they can develop better ways to support cell transplantation. Additionally, the role of various factors enhancing cell survival has been explored.

To conduct this rapid systematic review relevant literature was retrieved from three databases PubMed, Scopus, and Web of Science. Three additional peers participated in the initial database search; this is followed by individual screening of papers. In this review, five types of brain disorders were investigated using mice: Alzheimer's, Huntington's, multiple sclerosis, jaundice, and epilepsy. A variety of cells were also transplanted into the mice's brain, including neural progenitor cells and mesenchymal stem cells.

Immunocytochemistry was used to assess survival rates of transplanted cells post-transplantation. The conducted studies revealed that immune rejection of transplanted cells is a significant reason why survival rates in a mouse model of Huntington's disease are as low as 1.3%.[2] The co-administration of drugs with immunosuppressant properties such as Fingolimod has improved cell survival rates in mice models of multiple sclerosis.[3]

This review concludes that poor cell survival post-transplantation cannot be attributed to a single main factor, but rather to a combination of factors. In over 98% of reviewed studies, the primary therapeutic implication of cell transplantation therapy for neurodegenerative disorders was to improve cognitive impairment.

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A rapid review on the survival of Listeria monocytogenes biofilms on surfaces in the food industry

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Listeria monocytogenes is a foodborne pathogen that is responsible for causing listeriosis, which is a particularly detrimental infection if contracted by pregnant or immunocompromised patients[1]. This bacterium is of concern to the food industry due to its ability to develop higher resistance[2] and survive conditions intolerable to other bacteria[3]. The overall aims of this rapid review were to explore factors influencing *L. monocytogenes* biofilm survival on surfaces in the food industry and to evaluate current and potential management strategies.

PubMed and Scopus were utilised to conduct the literature search and results were exported to excel. The papers were then screened against the inclusion and exclusion criteria before being removed accordingly. All relevant papers underwent a quality and risk of bias assessment and critical appraisal, final papers then had data extracted and were analysed.

This review contains a sum of 17 papers as a result of the screening process. Overall, multiple studies suggested biofilm production to be greater at higher temperatures and at prolonged incubation periods. Furthermore, strain variation appeared to have a great effect on the ability to form biofilms in both single and mixed species biofilms. 3 studies focusing on potential management strategies showed a level of effectiveness

including methods such as enzyme use, bacteriophage P100, and nisin and neutral electrolysed water as a combination treatment.

This review explored new possible treatments effective towards *L. monocytogenes* biofilms and some of the contributing conditions responsible for increased growth. However, this review highlighted the need for using standardised methodologies to palliate the wide variation in cultivation and measurement methods of biofilms across the included studies. Therefore, further research is required to test these conditions in a standardised format to obtain comparable and valid conclusions and determine optimum environments for biofilm growth.

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Evaluation on how Pharmacist Independent Prescribers expand their scope of practice and their views on the role of a Designated Prescriber Practitioner

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The introduction of pharmacist independent prescribing in 2007[1] has meant that pharmacist independent prescribers (IP) can prescribe drugs for any condition within their scope of practice. The lack of regulation to expanding scope of practice means the aim of this study is to ascertain how independent prescribers in Wales are using their prescribing qualification, and have they expanded their scope of practice. Instead of a Designated Medical Practitioner the General Pharmaceutical Council now allow a Designated Prescriber Practitioner to supervise a trainee prescriber[2]. This study in collaboration with Health Education and Improvement Wales aims to assess the views of IPs on this matter.

Due to the numerical nature of the study, a questionnaire was designed last year by Cardiff university staff and HIEW from anonymised scripts of qualitative interviews undertaken with community IPs. The questionnaire was distributed in November via social media and data was analysed descriptively and downloaded into Microsoft Excel to create graphs.

Results showed IPs use many methods to record competence in their expanded field of practice, these included: CPD portfolio's, E-learning certificates, and case studies. Results showed that 76% of IPs expanded their original scope of practice, whereas 24% did not. The study showed that 36% of respondents answered 'Yes', 34% answered 'Maybe' and the 30% that 'No' to becoming DPPs stated they didn't feel competent in training another individual in skills that would be better explained by a DMP.

The study concludes that in order to overcome barriers faced by IPs more funding should be given to guide IPs and facilitate expansion in a new scope of practice. In order to increase competence and confidence of IPs in diagnostic skills, official training in this aspect should be given by HEIW and the Welsh Government. Thus, subsequently increasing the interest of IPs in becoming DPPs.

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An evaluation of the switch from Heparin to Taurolock Hep500 as a lock solution in tunnelled haemodialysis central venous catheters in South West Wales Renal Unit

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Catheter occlusion is a classic problem with central venous catheters (CVCs), increasing the risk of subsequent complications.[1] Prophylaxis with catheter lock solutions (CLS) is required; guidelines recommend a CLS with combined anticoagulant and antimicrobial properties, yet no "gold standard" has been identified to date.[2] This research aimed to investigate whether switching CLSs from heparin to Taurolock Hep500 in Southwest Wales reduced catheter occlusions seen with CVCs.

Data pertaining to all CVCs constructed for haemodialysis within 01/08/2018 and 01/08/2021 were extracted from Vital Data. Lines were divided by initial line-locks, forming two groups: heparin and Taurolock Hep500. The heparin group was further sub-divided into those maintained on heparin and those that switched to Taurolock Hep500. The incidence of thrombotic complications in three resulting groups - heparin-only (98 lines), heparin-switch (80 lines) and Taurolock Hep500 (139 lines) – were evaluated.

Catheter occlusion was significantly greater in the Taurolock Hep500 group than the heparin-only group with 1.13 and 0.42 alteplase administrations per 1000 catheter days respectively (odds ratio 3.94; 95% CI 1.87, 8.31). Line removals due to thrombosis were 5/139 and 1/98 in the Taurolock Hep500 and heparin-only groups respectively, a significant difference (odds ratio 3.62; 95% CI 0.42, 31.48). However, time to first alteplase dwell was greater in the Taurolock Hep500 group (136.50 days cf. 88 days with heparin-only).

These findings oppose the switch to Taurolock Hep500 due to greater rates of thrombosis, which in turn leads to higher costs when compared to heparin-only CLS. Surrounding literature is controversial and highlights the need for more robust studies to confirm Taurolock Hep500's anti-occlusive properties and to offer an explanation as to why Taurolock Hep500 lines required more thrombolytic therapy.[3,4] It is recognised that analysis of the impact of the switch of CLS on infection rates, alongside thrombotic complications, is needed to provide a complete picture.

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The use of lateral flow self-test in COVID-19 infection screening: a rapid review of the literature

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Lateral flow self-tests (LFTs) are viral antigen tests for the detection of SARS-CoV-2, the virus that causes COVID-19 infection.[1] LFTs are employed in mass testing schemes in many countries because they are relatively low cost and can produce a result within 30 minutes without laboratory interventions.[2] However there are mixed opinions on the usefulness of LFTs being used as a self-test.[3] The aims of this review were to review literature up until 31st October 2021 then used the information to determine the accuracy and usability of LFTs when performed by untrained individuals and also to determine whether the limitations of LFTs would prevent them from being used in the future mass-testing campaigns.

Searches were conducted on 3 different online databases, using PRISMA principles, to identify studies comparing the accuracy and usability of COVID-19 self-diagnostic tests with PCR tests. The risk of bias was assessed. Data reporting the accuracy, ease of use and comfortability were analysed.

Thirteen studies were identified. LFTs were more sensitive in detecting COVID-19 patients who had a high amount of SARS-CoV-2. The overall specificity of LFTs was much higher and more consistent than the overall sensitivity. Anterior nasal swabs demonstrated the highest overall sensitivity. Sample collection, processing and transfer to the LFT were reported to be an issue in several studies. None developed a nose bleed or reported strong pain.

LFT is a good screening tool but not a good diagnostic tool for COVID-19 because it has a low sensitivity and high specificity. It is particularly beneficial when used to test a big population where the majority do not have COVID-19. The majority of users found them easy to perform and did not experience any difficulties or pain. Therefore LFTs is a good choice for at-home early screening for COVID-19 infection.

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Stability of Vitamins and Lipid Emulsions in Parenteral Nutrition

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Parenteral Nutrition (PN) is an infusion of nutrition that consists of amino acids, carbohydrates, fats, electrolytes, vitamins and trace elements for patients who cannot obtain sufficient nutrients through oral or enteral route. Lipid Emulsions (LE) serve as a vital cellular energy source[1] while vitamins are important for growth and development. Due to the immensely complex composition of the admixture, numerous reactions that influence the stability of the chemical compounds arise during the preparation, storage, transportation and administration of PN. In this rapid review, there is an outline of stability issues associated with LE and vitamins in PN and the effects on patients requiring PN support.[2]

Four databases: Medline (Ovid), Web of Science, Science Direct and Scopus were used to search for literature using defined key terms. Papers were extracted into EndNote X9 and screened for eligibility. Results were narrowed down following the PRISMA flow process and twelve papers were included for analysis. The final papers were assessed for risk of bias using the Joanna Briggs Institute critical appraisal tools.

The findings show that Vitamin A is the most light-sensitive vitamin added to PN admixtures and Vitamin C is rapidly oxidized by air.[3] LE was indicated to have a protective effect on the stability of multivitamins while vitamin E was proven to counteract lipid peroxidation of LE in PN. Other PN components such as amino acids, glucose and trace elements also affected the stability of LE and vitamins.

Further studies are needed to investigate whether stability issues can be minimized by mixing both components to ensure patients receive optimum nutrients. Controlling chemical and physical conditions plays integral role in reducing PN instability. Ongoing research on the development of new formulations PN and Home Parenteral Nutrition should be encouraged to deliver a more stable and safe means of PN in the future.

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Are SLC39A zinc transporters a good target for breast cancer: A rapid review.

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There is a clinical need for therapies to target aggressive breast cancer such as metastatic or tamoxifen resistant breast cancer[1]. Aberrant expressions of zinc and its transporters has been implicated in various cancers. The aim of this review is to determine if ZIP transporters are a viable target in breast cancer.

This rapid review analysed 134 publications from four online databases. Using an inclusion and exclusion screening criteria, seven papers, that were relevant were selected. These papers were then analysed, and pertinent information was extracted before they were critically appraised using an appropriate research paper checklist to identity any bias present.

Findings showed that ZIP6, ZIP7, ZIP9 and ZIP10 are all implicated and have a role in breast cancer. Clinical data analysis from published literature and independent research from the GEPIA database confirm that the upregulation of ZIP6, ZIP7 and ZIP9 were of statistical significance; however, the upregulation of ZIP10 was elevated but failed to reach statistical significance.

Surrounding literature supported the findings and helped confirmed that these ZIP transporters play a key role in the progression of breast cancer. ZIP6 and ZIP10 form a heteromer, essential for mitosis in the cell[2]. Further research described how ZIP7 upregulates signalling pathways which have been seen in more aggressive cancers and there is evidence that ZIP7 is prominent in tamoxifen resistant breast cancer[3]. Other studies explained the apoptotic mechanisms of ZIP9 and detailed other agents that could activate ZIP9[4]. This review concludes that ZIP6, ZIP7, ZIP9 and ZIP10 could be good potential drug targets. Further research must be undertaken to find the crystal structure of these ZIP transporters and/or, antibodies to target ZIP6 and ZIP10 to prevent cell division. An agonist must be developed to target ZIP9 and further exploration of the CK2 or other small molecule inhibitors to target ZIP7.

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ASSESSING THE STABILITY OF THE MONOCLONAL ANTIBODY RITUXIMAB THROUGH PHYSICAL STABILITY TESTING AND DEVELOPMENT OF A HPLC METHOD TO TEST IN USE STABILITY

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Monoclonal antibodies (Mabs) are the forefront of cancer targeted therapy.[1] However, they are prone to degradation due to their large proteinaceous nature.[2] Currently, the stability data on Mabs, including transport and/or storage, is limited but has great relevance to patients and clinicians. Undoubtedly the stability of Mabs could affect the efficacy of the treatment and hence, the outcomes for patients. Therefore, this study aimed to develop a high-performance liquid chromatography (HPLC) method to separate and quantify Rituximab and test its stability through physicochemical assays.

The HPLC method described by Navas, N et al was used as a reference[3], to initiate the method development. Rixathon represented the Rituximab standard and was diluted with 0.9% sodium chloride. The chosen variable was temperature thus, the experimental samples were held in a laboratory with a fluctuating room temperature and the control samples were left in the refrigerator. These were tested by particle count and pH, at Day 0, 7, 14 and 21 and were also HPLC analysed.

Unfortunately, the HPLC method failed to ensure peak resolution and could not be validated according to ICH guidelines.[4] Therefore, Rituximab could not be reliably quantified. However, the method is stability-indicating. The results of the physicochemical stability assays are supportive and indicate the degradation of Rituximab with the effects of temperature. Moreover, the control sample exhibited signs of instability at Day 21. Surprisingly, this contradicts the recommended shelf life published by the electronic medicines compendium (EMC).

Further research is necessary in order to validate the method and separate the peaks and fragments. Thereafter, it will be possible to achieve an accurate quantification of Rituximab. Evidently, the assays prove the instability of Rituximab and since the full molecule is required for the desired therapeutic effect, this data warrants urgent review into the management of Rituximab to enhance treatment outcomes.

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Determination of cell viability within 3D printed epidermal skin models

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The field of skin research has been transformed by the advancement of 3D bioprinting for the fabrication of skin models.[1] However, cell death during and post-printing is an ongoing problem.[2] This project aimed to design a method for determining cell viability post-printing using live-dead stain[3], which will be useful for the optimisation of bioprinting techniques in the future.

A custom-built bioprinter was used to print multi-layered models with alginate bio-ink following the droplet-based bioprinting approach.[4] The staining procedure was adjusted in a stepwise manner to minimise its impact on model structural stability. Viability of HEK293 cells encapsulated within printed models was assessed immediately post-printing and again after 24hrs through addition of live-dead stain solution (diluted with PBS).[3] Fluorescence was captured using EVOS imaging performed after the models were incubated for 60 minutes with the stain.

The key finding was that live-dead stain can penetrate through alginate to stain cells within a 3D printed model, with a good level of stain penetration observed after 60 minutes incubation with the stain. Live-dead stain diluted with PBS was found to trigger rapid disintegration of the structure when added directly after printing. Also, after 24hrs within a printed model, live-dead staining indicated that all encapsulated HEK293 cells were dead.

These findings support the concept of adding live-dead stain post-printing. They indicate that an incubation time of 60 minutes is sufficient to allow diffusion of live-dead stain through alginate. The use of PBS in the stain solution disrupts droplet gelation and causes disintegration of 3D structure, due to its pH buffering effects, so the use of DMEM media instead of PBS should be trialled. Possible reasons for cell death at 24hrs include prolonged droplet gelation, through making essential nutrients inaccessible to cells[2], although further investigation of other factors is needed.

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The prospects of energising artificial bilayers using bacteriorhodopsin

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Artificial cells are mimics of biological cells and have applications in many fields including medicine. Various proteins and channels can be reconstituted within these artificial membranes, creating new functions which are not found in natural cells. Investigation of these protein functions can potentially lead to the development of new uses.[1] One protein called bacteriorhodopsin can be incorporated into artificial membranes and translocate protons converting light energy to chemical energy. This can then be used to energise the cell system as next generation of smart materials that may find uses in diagnostics and drug delivery.[2] The main objective of this review is to determine how much work bacteriorhodopsin is feasible to do and whether further research is needed.

Searches were conducted on several online databases: Embase, Medline and Scopus. Inclusion criteria of qualitative data for bacteriorhodopsin activity was used to select the final publications. All the included studies measured the activity of bacteriorhodopsin in terms of the electrical current signals generated. These values were compared to determine which study reported the largest currents. The PRISMA flow diagram shows the number of papers retrieved from data searches was narrowed down from 85 to 16.

Analysis of the data determined that current values for lipid bilayer membranes ranged from 0.002 to 2.6 nA. The largest stationary currents were reported in solid supported membranes however values obtained from papers investigating non-lipid membranes were multiple fold greater than lipid membranes. This shows that membrane composition is an important factor which may affect the activity of bacteriorhodopsin, with membrane integrity or porosity with different platforms also providing an alternative explanation. Other parameters may also impact on signals produced such as type of lipid used, salt condition and light intensity however the variable space is too large to come to a conclusion.

The data within this review attested to the ability of bacteriorhodopsin to translocate protons when illuminated by a light source. However, as variable space was quite large, further research should be conducted to determine the optimal conditions of the parameters mentioned above and whether bacteriorhodopsin can be harnessed to energise artificial cells.

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Exploring the Opinions of Health Care Professionals in Primary Care: Is There a Place for Antibiotic Delabelling in the Community?

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In the UK, 10% of the population have a "Penicillin allergy", however, 90% are mislabelled and can safely receive Penicillins.[1] Prescribing alternative antibiotics allows for a selective advantage for mutated bacteria (increasing morbidity/mortality), and loss of healthy gut flora (resulting in *C. difficile* colitis).[2,3] These problems also increase hospitalisation length, which, when combined with the expense of alternative antibiotics, demonstrates misdiagnosed Penicillin allergies are both a public health concern and an expensive issue for the NHS.[4] In Wales, "delabelling" (removing false Penicillin allergy labels) is only offered in hospitals and is progressing slowly. This project, therefore, aims to explore the possibility of transferring delabelling into Primary Care.

A qualitative approach was utilised to produce the detailed data needed. Following ethics approval, semi-structured interviews were conducted with health professionals, transcribed *ad verbatim* and thematically analysed to elicit key themes from the views of Health Care Professionals within Primary Care.

Data from eight interviews suggested a positive outlook towards delabelling, particularly via history taking (assessing an antibiotic allergy label's appropriateness based on the patient's previous history), whereas concerns regarding patient harm were more intense when delabelling by Direct Oral Challenge (providing a low dose of Penicillin and observing for a reaction). Barriers mentioned included lack of patient/staff education and time needed to conduct the tests. The main enablers were standardised protocols and training to ensure effective and safe delabelling and funding for providing a new service.

Large scale results cannot be determined; further opinions must be assessed before the transition of delabelling into Primary Care. Therefore, a questionnaire has been developed from the interview data. This tool will allow more generalisable data to be collected, and could be instrumental in the planning and development of a Primary Care delabelling service, if it is demonstrated to be feasible.

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An Explorative Study into the Trends of Broad-Spectrum Antibiotic Prescribing in Primary Care in Wales at Health Board and Cluster Level between 2015 to 2021.

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Antimicrobial resistance threatens common infections becoming high risk again and costing the healthcare system trillions of US dollars globally. The 5-year UK national plan emphasises inappropriate antibiotic prescribing in primary care as a leading issue.[1] The All Wales Medicines Strategy Group (AWMSG) developed National Prescribing Indicators (NPIs) to promote optimised prescribing in specific therapeutic groups including antibiotics.[2] This was chosen with the aim of identifying prescribing patterns and investigating possible correlation with deprivation data which may give rise to health inequalities.

Anonymised quantitative prescribing data was provided by AWTTC using the Comparative Analysis System for Prescribing Audit (CASPA) database, presented as number of itemsper1000 patients at cluster level and accounting for differences in population size. This was changed to itemsper1000 prescribing units (PU) to account for the higher health care needs of older patients. Welsh Index of Multiple Deprivation (WIMD) 2019 was averaged for each cluster based on eight domains. Statistical analyses were performed to assess significance of correlation between income deprivation and prescribing data.

Temporal and spatial trends were identified through analysis at a health board and cluster level. Principle findings included a general decrease in antibiotic prescribing with the exception of nitrofurantoin and azithromycin. A cluster with consistently high prescribing of certain antibiotics was Afan in Swansea Bay health board. Antibiotics that showed the highest decline in prescribing after COVID lockdown and social distancing rules were introduced were clarithromycin and doxycycline.

For clusters like Afan further insight may be gained from more detailed investigation and collection of data with a focussed audit at surgery level for enhanced data analysis. Implementing read codes that show the indication for each antibiotic prescription dispensed in community would be a great opportunity to assess prescribing quality as well as quantity.[3] Future research can build upon ideas discussed in this report and determine whether similar trends exist in narrow-spectrum antimicrobial prescribing.

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Exploring the barriers and influences to studying pharmacy at Cardiff University

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Concern has risen regarding the shortage of pharmacists as demand and changes for the profession grow.[1] *Pharmacy: Delivering a Healthier Wales* sets future goals for pharmacy professionals to aid the long term-plan of *A Healthier Wales*, resulting in an increased need for pharmacists to provide further services and their presence in all departments. Pharmacists were added to the Home Office's shortage occupation list in March 2021 due to the decrease in pharmacy graduates and increase in service demands.[2] Pharmacy schools are becoming reliant on clearing and lowering entry grades to increase the number of students on the course, and education chiefs are concerned about the popularity of the MPharm.[3] Therefore, this study aims to explore both the influences and barriers that exist to studying pharmacy at Cardiff University.

The research required the exploration of personal perspectives, a qualitative research method was therefore used.[4] Eligible participants were purposively sampled. Online, one-to-one, semi-structured interviews were then conducted after obtaining ethics approval and signed participant consent forms. All interviews were both video and/or audio recorded, these were thematically analysed to construct themes.

Identified influences included family and friends, career pathways and roles, previous education, course features, work experience and the reputation and publicity of Cardiff School of Pharmacy. The two main barriers were ignorance and the inferiority of pharmacy. Future promotion was discussed by the participants, and better promotion to key stage four and five pupils was recommended.

Intrinsic motivators appeared to be slightly more influential than extrinsic motivators for the included participants. Current literature contains varying opinions regarding the extent of each influence. The barriers identified are commonly seen in the public. The findings require utilisation to develop a further data collecting tool to gain more generalisable findings.

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Paediatric pharmacovigilance: a rapid review investigating interventions that could increase the reporting of adverse drug reactions in children

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Reporting adverse drug reactions (ADRs) is essential to identify safety concerns regarding medications.[1] Children are at a greater risk of experiencing ADRs as they respond to medication in unpredictable ways[2] and do not generally participate in clinical trials.[3] Despite this, reports made for children in the UK to the Yellow Card Scheme (YCS) are particularly low.[4] Therefore, methods to increase paediatric ADR reporting are essential to gain a better understanding of the effects of medication in this population. This rapid review aims to summarise the findings of research discussing interventions to increase paediatric ADR reporting and construct recommendations on interventions that the YCS could utilise to do this.

A structured literature search, to identify relevant articles was conducted using the Medline, Embase, Emcare, Global Health, Web of Science and Scopus databases. Primary research articles specific to the reporting of adverse reactions to medication or vaccines in children under 18 were eligible for inclusion and a PRISMA flow diagram was produced to convey the search process. Relevant data was extracted from the included articles and each study was critically appraised to determine their quality.

16 articles, conducted in 11 different countries, were included in this review and these either discussed interventions to increase spontaneous reporting or interventions to be used alongside spontaneous reporting to actively encourage reporting for specific medications or vaccines. Each study produced promising results and therefore, each intervention could potentially increase paediatric ADR reporting.

Despite the promising results, most of the studies were of moderate quality, many did not include a control to appropriately convey efficacy, most were conducted outside the UK and those conducted in the UK were not particularly recent studies. Therefore, each intervention would need to be trialled in children under 18, to determine their current feasibility and cost-effectiveness in the UK.

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The Efficacy of Taurolock Hep500 Compared to Heparin as a Line Lock Solution in Tunnelled Central Venous Catheters for Haemodialysis in South West Wales Renal Units

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Catheter-related bloodstream infections are severe nosocomial infections associated with increased mortality rates and prolonged hospital admissions in haemodialysis patients.[1] Effective preventative strategies must be utilised to reduce the severity of these complications. The UK Renal Association has emphasised the importance of using a combination of an antimicrobial and anticoagulant line lock solution rather than heparin, which was previously used to maintain catheter patency.[2] The purpose of this research was to establish whether Taurolock Hep500 was clinically more effective at reducing the incidence of infection and improving catheter survival compared to heparin.

Data was retrieved from Vital Data (VD), with every tunnelled line inserted between 01/08/2018 and 01/08/2021 being considered for inclusion in this study. The dataset was subdivided based on initial line lock resulting in a heparin group (98 lines) and a Taurolock Hep500 group (139 lines). A secondary dataset comprising lines switched from heparin to Taurolock Hep500 over the life of the catheter was also created. The outcomes measured included assessing both datasets for infective complications and length of catheter survival.

The incidence of infection was significantly higher in the primary heparin group than in the Taurolock Hep500 group - 2.09 vs 0.55 infections per 1000 catheter days (odds ratio 0.17; 95% CI 0.09 - 0.63, $P < 0.0001$). Catheter removal due to infective complications was significantly higher in the primary heparin group - nine lines were removed compared to three in the Taurolock Hep500 group (odds ratio, 0.24; 95% CI 0.06 – 0.92, $P = 0.03$).

The results show the clinical benefit of Taurolock Hep500 line locks in preventing infections in haemodialysis patients. The findings are consistent with other studies demonstrating taurolidine's efficacy over anticoagulant only lock solutions. [3-4] Nevertheless, further research is required to understand how the switch to Taurolock Hep500 impacts other clinical outcomes, for example, thrombotic complications.

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Is it appropriate to switch Salbutamol Metered Dose Inhalers (MDIs) to Dry Powder Inhalers (DPIs)? - A Rapid Systematic Literature Review

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Salbutamol Metered Dose Inhalers (MDIs) are the single largest source of carbon emissions with respect to prescribing medicines in the NHS and are vital for relief of bronchoconstriction in patients with asthma.[1] However, their environmental impact is significant compared to other inhaler device.[2] The Dry Powder Inhaler (DPI) is a low carbon alternative but there are concerns regarding its efficacy in acute severe bronchoconstriction due to requirements of patients to overcome the resistance of the DPI device.[3] This study aims to identify whether DPIs provide comparable relief of bronchoconstriction to identify if a switch from MDI to DPI is appropriate.

This study employed a rapid systematic review methodology. To ensure a wide scope of results were returned, four databases were used: EMBASE, Medline, Web of Science and Scopus. No date restrictions were made

since there have been no major changes in MDI and DPI use. Primary research papers that met the inclusion criteria were analysed.

Twenty randomised controlled trials demonstrated that DPIs provide relief in all severities of bronchoconstriction, notably in acute severe asthma. Furthermore, the Forced Expiratory Volume in 1 second (FEV1) increased irrespective of inhaler type and the addition of a spacer with an MDI did not make it superior.

The literature suggests it is safe and appropriate to switch salbutamol. Guidelines can be amended to encourage the switch from MDIs to DPIs to reduce MDI prescribing. This will result in an associated reduction in carbon emissions for the NHS and healthcare providers globally. This finding was surprising as it was anticipated that the use of DPI in acute severe asthma would not be appropriate, since patients were not expected to be able to overcome the intrinsic resistance of the DPI device and obtain relief. However, our concerns were confounded in this scenario.

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Factors affecting the flow rate accuracy of elastomeric infusion pump: a rapid review

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An elastomeric pump (EP) is the simplest type of ambulatory infusion pump (AIP) which relies only on pressure to operate and infuse various types of drugs and it is designed especially for ambulatory settings.[1] It is crucial to ensure that an EP maintains an accurate flow rate of delivery to avoid any potential adverse consequences for patients.[2] This rapid review aims to determine the factors that influence the delivery flow rate of EPs from the empirical literature and to make recommendations to improve accuracy of delivery.

Three validated databases were searched (PubMed, SCOPUS and Medline) to find relevant literature reporting on factors affecting the flow rate accuracy of EPs. Keywords were used to develop the search area and find studies that satisfied the stated inclusion criteria. They were critically appraised using a laboratory experimental-based research checklist and references were managed using Endnote software X9.

14 out of 1,935 eligible studies were included in this rapid review. This review summarises the study design, factors affecting flow rate accuracy, EPs tested, analytical methodology and key findings. The following factors were found to significantly cause inaccurate rate delivery: temperature, viscosity, hypobaric and pressure gradient.

Flow rate becomes proportionally inaccurate with extreme temperatures. The rate is significantly reduced when drugs with high viscosity are included. Changes in pressure may cause an imbalance in pressure on pump parts and, therefore, the rate may be significantly affected. Repeated and intentional overfilling were found to have an insignificant impact on flow rate accuracy. However, each EP is manufactured differently using a variety of materials and thus has its own flow rate profile, therefore, it is not possible to apply one result to another EP and each should be tested individually to ensure accuracy. Overall, future researchers should examine EPs, especially structural developments to maximise accuracy, by controlling the flow rate when exposed to potential factors.

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The effect of PCSK9 inhibitors on low density lipoprotein cholesterol levels in patients with atherosclerotic cardiovascular disease compared to standard treatments. A rapid review

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality worldwide.[1] Patients with ASCVD have higher incidence of major adverse cardiac events (MACE) associated with elevated low-density lipoprotein cholesterol (LDL-C) levels. Three proprotein convertase subtilisin/ Kexin type 9 inhibitors (PCSK9i) – two monoclonal antibodies and one RNA silencer – are the latest treatments available.[2] This review aims to investigate the efficacy of PCSK9i on LDL-C levels and subsequently MACE in patients with established ASCVD.

Three databases (Embase, Medline and PubMed) were searched for papers published after June 2004 to find suitable studies for inclusion in this rapid review. Papers included must have been full text articles written in the English language, published in a peer reviewed journal and investigating currently licensed PCSK9i against standard treatments in patients with established ASCVD. Papers were screened by title and abstract first, then full text. Data was extracted from methods, outcomes, discussions, results tables and figures to be analysed in this review. A PRISMA diagram was used to display a record of papers included/ excluded. Following selection 11 papers were critically appraised and assessed for bias using the relevant JBI and CASP checklists.

The 11 papers included consisted of three randomised controlled trials, six predefined secondary analyses and two observational cohort studies. Within this, two papers investigated Inclisiran, five investigated evolocumab, three investigated alirocumab and one did not specify PCSK9i investigated over a one-to-two-year duration. All papers found PCSK9i treatments in combination with statins lowered LDL-C levels on average by 50%. Six papers found a lower incidence of MACE in PCSK9i groups compared to placebo.

Currently licenced PCSK9i in large scale trials are highly effective at lowering LDL-C levels when in combination with statin treatments. However, there is a need for long term trials investigating the impact of treatment on mortality rates and potential safety concerns.

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The reconstitution of the membrane protein PFO into droplet interface bilayers

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Pore-forming proteins (PFPs) are of particular interest in synthetic biology as researchers utilise their cell penetrating abilities to allow the passage of a variety of biological molecules and ions across a lipid bilayer.[1] In this field, artificial cell membranes such as droplet interface bilayers (DIBs), provide an easy and quick approach for studying these kind of proteins.[2] Understanding the mechanism of protein insertion into a bilayer would be a scientific advance, as it offers numerous advantages such as understanding membrane protein mechanistics and mode of action, which may result in the identification of potential disease treatments.3

Cholesterol dependent cytolysins (CDCs), are a family of pore forming proteins used in synthetic biology that bind on the cell membrane in the presence of cholesterol.[4] Perfingolysin O (PFO) was selected for this study due to it forming a large pore for the passage of proteins. However, conditions for its successful reconstitution in artificial membranes remain poorly studied therefore this makes it novel research. In this research, a rapid review of the literature was conducted in order to identify optimal experimental conditions for reconstituting the pore-forming protein Perfingolysin O (PFO) in a droplet interface bilayer (DIB), which could then be evaluated experimentally.

Medline (Ovid), Google Scholar and Scopus were the three databases used for study selection which led to the inclusion of 16 research papers. Once the studies were assessed for eligibility, they were further evaluated

using Joanna Briggs Institute tool (JBI). Data retrieved from the included studies was the driving factor behind the designing of experimental procedures.

According to literature's experimental methods for PFO reconstitution, different lipid mixtures were evaluated for forming DIB membranes. A bilayer formed upon the contact of two aqueous droplets which had been immersed within a lipid in oil environment. When a bilayer formed, a voltage was applied, and protein reconstitution was assessed by electrophysiology. Electrophysiology measurements recorded the ion movement through individual membrane inserted pores.[2]

The most interesting results that suggested PFO reconstitution were found using a 10mM lipid mixture of DOPC, POPS and cholesterol at a ratio of 25:20:55, a protein concentration of 850nM, a buffer solution of 1 Molar KCl in 100mM MES at PH 5. The results of this project might not support a completely successful reconstitution of PFO into a droplet interface bilayer, but suggest the possibility of arc like structures facilitating membrane-pore formation. These are "immature pores" that are unstable and produce variable conductance due to the temporary flow of ions through the lipid bilayer.[5] Nevertheless, further research is needed to make the study of PFO more obvious which will progress synthetic biology methodologies to provide new perspectives in the assembly of transmembrane pores.[1]

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Exploring Health Inequalities links by relating Opioid Prescribing in Primary Care to Geographical and Temporal Trends within Wales

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Differences in prescribing can contribute to health inequalities. Health inequalities are avoidable differences caused by socio-economic status, deprivation, demographic factors, and location.[1]

National Prescribing Indicators (NPIs) were developed by The All Wales Medicines Strategy Group (AWMSG) and implemented to reduce health inequalities and promote rational prescribing.[2] NPIs for opioid prescribing are assessed in this study, focusing on evaluating opioid burden and tramadol prescribing in Wales. The aim of this study is to analyse primary care opioid prescribing data by primary care clusters and health boards within Wales and evaluate adherence to evidence-based recommendations.

Quantitative prescribing data between January 2016 and September 2021 was extracted from the Comparative Analysis System for Prescribing Audit (CASPA) database. This provided monthly opioid prescribing data for the 64 clusters in Wales and their respective health board. The opioids identified for inclusion in the study were determined by reviewing current British National Formulary (BNF) treatment summaries related to; analgesia and prescribing in palliative care.[3]

Analysis of prescribing data illustrated an overall decrease in levels of opioid prescribing in Wales. Betsi Cadwaladr was identified as the health board with the highest opioid prescribing levels across the data collection period compared to other health boards in Wales. Additionally, a steep decrease was observed with tramadol prescribing that resulted in morphine becoming the most dispensed opioid analgesic in 2017.

Despite a general decrease in opioid prescribing, health inequalities were observed by the geographical variation as there were differences in prescribing levels of opioids across all health boards. Furthermore, the decrease in tramadol prescribing can be explained by the classification change in 2014, highlighting that prescribers adhered to changes in guidance.[4] This study highlights key areas for future research and possible

interventions to reduce health inequalities. Informing and educating prescribers on concerns identified could lead to safer prescribing and possibly eliminate health inequalities.

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Are β-adrenoceptor antagonists an effective and beneficial treatment option in the management of Takotsubo cardiomyopathy? A Rapid Review

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Takotsubo cardiomyopathy (TCM), also referred to as “broken heart syndrome”, is when the heart muscle becomes suddenly stunned or weakened, characterised by a transient hypokinesis of the left ventricular (LV) apex in response to emotional or physical stress. The pathophysiology of TCM is not fully understood but catecholamine-induced myocardial toxicity following severe stress is the most supported hypothesis.[1] β-adrenoceptor antagonists (BB) have been proposed as a potential therapy for TCM, due to their blockade effects on catecholamines.[2] As there is no current evidence to suggest BBs should be a treatment for TCM, this review aims to evaluate the efficacy of BBs as a therapy.

Peer reviewed articles were searched from 01 January 2000 to 04 November 2021 using the databases Medline, Embase and Scopus. Clinical and experimental studies were screened as part of this review. Risk of bias and quality of included papers were assessed using CASP checklists, Joanna Briggs Institute and SYRCLEs critical appraisal tools.

Of the 1639 papers identified from the search, this review includes 5 clinical and 3 experimental studies. Results from the studies indicate short acting, selective β1-blockers significantly improve LV dysfunction (p values < 0.05), with a dose dependent effect. Also, BBs with intrinsic sympathomimetic activity (ISA) have a noteworthy role in TCM. No significant association between 30 day in-hospital mortality and BB administration was found (2.4% vs 2.0%, p=0.703; risk difference, 0.4%; 95% CI, −1.2% to 2.0%).[3]

Included studies indicate short-acting, selective β1 blockers have a beneficial role in TCM patients to some extent, however the value of treatment is still unclear due to the conflicting results found. The rarity of TCM limits the quantity of research that has been conducted in this field. Hence, double blinded, randomised controlled trials are needed to extend the findings of this review.

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Exploring the well-being, burnout, and mental health status of pharmacy students during the COVID-19 pandemic: A Rapid Review

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Coronavirus was declared a pandemic in March 2020[1]. To limit the spread of the virus, restrictions were implemented which have adversely affected the mental health of the general population[2]. University students' mental health has been a rising concern for society[3] with pharmacy students under particular stress due to the pressure to create a professional persona[4]. Aim: To provide a synthesis of recent research to assess the

impact that COVID-19 has had on factors relating to pharmacy students' well-being, burnout, and mental health.

Pubmed, Web of Science and Embase were searched to find current literature addressing the research aim. 333 studies were screened for eligibility based on inclusion and exclusion criteria, including published in the English Language between 11th March 2020 and 31st October 2021. After title and abstract review, 15 papers were included in the final review. These papers underwent critical appraisal and quality assessment; allowing for a narrative analysis to interpret the key characteristics and trends throughout.

This review summarises that there were high levels of depression, anxiety and burnout and low levels of well-being amongst pharmacy students during the pandemic. Therefore, the pandemic has had a definite negative affect on pharmacy students' mental health. However, some papers report positive experiences, thus the severity and the aspect of mental health affected is dependent on individuals and their circumstances.

High levels of mental ill-health were mirrored across studies assessing the impact on the general population and healthcare professionals. Due to the worryingly high levels of mental ill-health amongst pharmacy students, emphasis should be placed on providing more successful student support programmes. To gain a greater understanding, more studies with identical outcome measurement are required to undertake a meta-analysis, and longitudinal studies assessing pre and post pandemic should be conducted to identify trends and allow for preparation of future events.

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An assessment of stability of the monoclonal antibody rituximab in response to shear stress via a physical stability study and the development of a High Performance Liquid Chromatography Assay (HPLC).

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Rituximab, RTX, is a monoclonal antibody (mAb) licensed to treat non-Hodgkin's lymphoma and Rheumatoid arthritis[1]. Its large protein structure is vulnerable to physical and chemical degradation which could compromise stability thus hindering drug safety and efficacy[2]. This project aimed to create a validated stability testing protocol for use at St Mary's Pharmaceutical Unit (SMPU) through the development of a high performance liquid chromatography (HPLC) assay[3] and a physical stability study, focused on shear stress.

During method development, samples of RTX were analysed via HPLC instrumentation with alterations made to the conditions to optimise the assay. Validation was undertaken according to the International Council on Harmonisation (ICH) Q2(R1) guidelines[4]. The physical stability study used RTX at 2mg/ml in 100ml I.V. bags, these were inverted 20 times before being tested for their pH and particle count data on days 0, 7, 14, and 21.

Despite modifications, the HPLC assay could not be fully validated due to the RTX peak not resolving from other analytes in the HPLC run. However, the assay can be used as stability indicating as breakdown products could be detected with a comparative peak area decrease in RTX. Upon degradation it was observed that mAbs fragment retaining similar hydrophobicity to intact RTX making them difficult to separate via HPLC thus interfering with quantification[4]. Results of the physical stability study show RTX degrades in response to shear stress demonstrated through declining pH and the increasing number of small particles recorded on test days. By day 21 the control bag also showed degradation; SMPU store RTX I.V. bags for 30 days suggesting degraded formulations could be administered to patients. This has possible clinical implications including underdosing[1].

Therefore, this project recommends a review into the storage of RTX at SMPU, alongside bioactivity assays of the degradation products to confirm the research findings.

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MPharm4 students' perceptions and preparedness ahead of going into their foundation year training following the rise in digital teaching due to the COVID-19 pandemic.

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The COVID-19 Pandemic changed how educational material would be delivered to MPharm4 Cardiff University student's due to UK government guidelines implementing restrictions to reduce the transmission of the viral infection.

The pandemic resulted to higher education systems to expeditiously implement new e-learning and e-examinations to prevent the hinderance in educational development of student.[1] This study explored how different forms of digital learning may have prevented pharmacy students in their foundation year training preparations, but also how some of the remote methods of teaching may have prepared them even more than how traditional methods would.

This study used qualitative research as it was the most appropriate data collection methodology to explore student's thoughts and feelings on their experience as an MPharm4 students going into their placement year training. The recruitment process involved 'non-probability purposive sampling'[2] where students had to meet a specific inclusion criterion; Cardiff MPharm4 students whom applied for a foundation year placement for the 2022/2023 year.

This study identified four main themes where digital learning had affected their readiness for post-graduation in a positive or negative manner; *1*) *Online teaching methods and assessments 2) Communication changes between peers, teaching staff and Oriel 3) Disappearance of Placements prior to the Oriel application process 4) Direct support from both the university and Oriel in regards to direct preparation for their foundation year training.*

This study concluded that positives from limiting the pharmacy students to physical recourses, teachings and communication methods and implementing a more digital based approach can be useful to help improve the efficacy and preparations going into their foundation year training. This still requires trial and error from Universities and Oriel to identify which newly introduced aspects of online teaching are most effective to remain integrated post-pandemic. However, as of the participants of this study, the heavily weighted digital formats of teaching deemed to be a hinderance in their academic progression.

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Adipokine-tumour crosstalk, an opportunity for statin intervention?

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Obesity has long shown an epidemiological link to cancer. Exactly why this relationship exists is undetermined, but one theory proposed, is an imbalance of adipokine expression. Adipokines, are factors secreted by adipose tissue.[1] In obesity leptin is over-expressed while adiponectin is under-expressed.[2] Clinical studies have consistently shown statins can reduce cancer mortality and reoccurrence.[3] While pre-clinical evidence

suggests statins may be able to rebalance adipokine expression and that adipokine expression can influence several hallmarks of cancer. Here I have investigated whether statins have a role in mediating adipokine-tumour crosstalk.

Adipokine, cancer and statin related terms were searched through three databases: Ovid Medline, Scopus and Web of Science to retrieve relevant publications. These were subsequently screened and filtered leaving six relevant studies for data extraction and review.

The results were a mix of cell-based and animal-based findings. In cell models leptin activated downstream signalling molecules leading to increased cell survival and migration. The introduction of statins blocked leptin's cancer promoting effects. In mice models, statins were consistently shown to slow tumour progression. Blood samples from these mice showed statins were also able to reduce leptin levels and increase adiponectin levels, however these authors did not investigate the direct relationship between adipokines and cancer.

Wider pre-clinical evidence shows adipokines are to able activate a variety of cellular signalling cascades that promote the hallmarks of cancer. The evidence base focuses primarily on leptin induced pathways, however, adiponectin has been shown to activate various chemo-protective signalling pathways.[4] Clinical studies have drawn mixed conclusions about the relationship between firstly, adipokines and cancer, and secondly the effect of statins on adipokines. There is strong evidence suggesting statins do have a role as an adjuvant to cancer therapy, however the evidence linking adipokines to this relationship is limited and the findings are mixed, warranting further research.

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Assessing the mechanical properties of synthetic skin mimics that could be used to test the performance of Microneedle Array Patches

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Microneedle Array Patches (MAPs) are an emerging drug and vaccine delivery technology that promises to improve healthcare for millions worldwide. However no MAPs have achieved regulatory approval yet[3] partly due to a lack of performance tests that can verify the critical quality attributes of these novel devices.[2] This study analyses the mechanical properties of synthetic skin mimics using compression tests and compares them to human skin, with the intention of using a composite as a human skin surrogate in puncture performance tests of MAPs.

Compression tests were performed on four types of silicone with two different indenters (conical and flat) at high (8N) and low (2N) force. The force-displacement curves produced were compared to a matched set of data from human subjects. Composite silicone materials were then manufactured to better replicate the human data. The stability and uniformity of materials was also assessed to ensure reproducibility and examine potrential degradation of the material.

In general three of the silicones (EcoFlex 30, 35 FAST and GEL) were harder than human skin while a silicone-based foam (Soma Foama 15) was softer than human skin. Composites using a foam base with hard silicone top were manufactured to different thicknesses and better reproduced the human data. The hard silicone/foam composite that performed best matched the human data in 3 out of 4 compression test conditions. The uniformity of materials was good and stability varied depending on the material.

Further study is required to optimise the composition of an EcoFlex/Soma Foama composite to match human data in all four compression test conditions. Similar studies are needed to compare skin surrogates to human data for MAP testing.[3] The degradation profiles of these materials needs to be better understood to recommend suitable shelf lives. No artificial skin surrogate matched the human data in all four tests, but the thicknesses of

layers could be refined to accomplish this in a future study. These materials proved to be suitably reproducible for this application.

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Evaluation of tetrazole compounds to combat the challenge of drug resistance in the therapy of invasive fungal disease: a rapid systematic review

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Invasive fungal disease is an increasing global health issue, accounting for substantial morbidity and mortality worldwide[1]. With emerging resistance to current available antifungal therapies[2], the treatment of invasive fungal disease remains a challenge, thus the need for novel antifungal therapies has become vital. This rapid systematic review aims to evaluate if the novel antifungal class tetrazole, is a potential therapeutic option for the treatment of invasive fungal disease and if further research is warranted.

The databases Scopus, Web of Science and PubMed were consulted to find literature from the past 10 years that evaluate the *in vivo* and/or *in vitro* antifungal activity of tetrazole derivatives. The publications were extracted to EndNote X9, where they were screened for their eligibility against the inclusion and exclusion criteria, highlighted using a PRISMA flow diagram. Final publications were critically appraised using the SYRCLE risk of bias tool for *in vivo* studies, and data was extracted and analysed.

18 studies were included for final review following the eligibility criteria screening, including 11 *in vitro*, 6 *in vivo* and 1 *in vitro* and *in vivo* study. The *in vitro* studies assessed minimum inhibitory concentrations, and the *in vivo* studies assessed parameters such as survival, fungal burden and plasma concentrations.

Overall, it is suggested by every study included in this review that the novel antifungal class tetrazole displays potential to be a future therapeutic option for invasive fungal disease, even if the causative fungi possess antifungal resistance. The studies also suggest that tetrazole derivatives exhibit comparable or superior antifungal activity compared to current available antifungal agents, due to their favourable safety profiles and high selectivity. Despite this, further research must be conducted to investigate the compounds *in vivo* activity on human subjects, with fungi bearing varying susceptibility levels, to gain further insight into the pharmacokinetic and pharmacodynamic properties.

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Could SLC39A transporters be a good target for pancreatic cancer?

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The dysregulation of zinc homeostasis is becoming increasingly implicated in cancers.[1] A possible cause of this dysregulation is the under and over expression of zinc transporters such as the SLC39A (ZIP) family. Pancreatic cancer is the 4th leading cause of cancer deaths for both men and women[2] and consequently, more effective therapies are necessary. This rapid review aims to determine if SLC39A (ZIP) transporter dysregulation is involved in pancreatic cancer and subsequently whether this dysregulation is significant enough to provide a therapeutic target.

A rapid review was conducted. A search strategy was developed to extract relevant literature from 5 electronic databases: Medline, Scopus, Embase, PubMed and Web of Science. The resulting literature was screened against an inclusion and exclusion criteria to assess their eligibility. 9 final papers resulted from this analysis

and subjected to critical appraisal. Relevant data was extracted from the studies to make well informed conclusions relating to the rapid review questions.

3 papers found ZIP3 to be depleted in pancreatic cancer and in the PanIN lesion, which is a precancerous lesion from which invasive pancreatic cancer begins.[3] The rest of the papers found ZIP4 to be upregulated in pancreatic cancer. One paper suggested that overexpressed ZIP4 could be used as a diagnostic marker. While other papers suggested the overexpressed ZIP4 was responsible for allowing the progression of the cancer.

Whether ZIP3 is a good target for pancreatic cancer remains inconclusive. When searching the clinical patient data ZIP3 was actually found to be upregulated not downregulated like found in the rapid review. However, the rapid review found that ZIP4 was upregulated in pancreatic cancer and this was supported by clinical data found in GEPIA. Therefore, it is possible it could be a target for pancreatic cancer.

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Why pharmacy? An exploration of the influences and barriers to studying pharmacy at Cardiff University.

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In 2019, plans were put forward to change how care will be delivered within the NHS, as the Welsh Pharmaceutical Committee looks to *'transform the role and contribution of pharmacists'*.[1] This means that instead of relying on secondary care and hospital settings, the provision of care will be shifted *'closer to home'*, which will increase the demand for pharmacists within and around the Community.[2] With this in mind coupled with the current National Shortage of Pharmacists[3], this project aims to explore the influences and barriers to students studying pharmacy at Cardiff University, in order to maximise the workforce.

Due to the exploratory nature of the study, qualitative one-to-one semi strucutred interviews were chosen as the primary data collection method. Non-probability purposive sampling was used to recruit particiants to ensure they met the study inclusion criteria (1st year pharmacy students in Cardiff University). Interviews were audio and video recorded and transcribed verbtim. Data was thematically analysed to identify themes and sub-themes.

A total of 8 participants were recruited for the sample, and 5 main themes were identified; Educational influence, Rescources, Misconceptions, Personal exposure and The future of pharmacy. Each of these 5 themes were split into 3 sub-themes, that portrayed as either influences or barriers to students studying pharmacy at university.

This research concluded that a misconception of pharmacy exists amongst the student population as the continuous comparison of the role of a pharmacist to that of a Doctor prevails as a major barrier. The misconception is primarily down to the lack of promotion of the degree, which leads to very little or no exposure to pharmacy for aspiring healthcare students. In turn, it leaves many potential pharmacy students choosing to study medicine as their preferred choice. Recommended promotions deducted from this research included the earlier exposure to pharmacy for students introduced through practitioner-student interaction.

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Evaluating the Safety and Efficacy of Sialic Acid Substrate Replacement Therapies in the Treatment of GNE Myopathy

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GNE myopathy (GNEM) is a rare disease characterised by progressive muscle wasting in the extremities. Patients gradually deteriorate and most eventually become wheelchair bound. Studies have suggested the cause of this muscle atrophy is hyposialylation of muscle glycans, due to mutations in the GNE gene. Currently, there is no licensed treatment for GNEM. However, sialic acid substrate replacement molecules have been proposed to restore glycan sialylation. This rapid review explores the potential of Aceneuramic acid, N-acetylmannosamine and Sialyllactose in the treatment of GNEM by investigating their efficacy and safety.[1]

Medline, EMBASE, SCOPUS and PubMed were searched for relevant literature and screened by pre-determined eligibility criteria. Both clinical and experimental studies were included, and all necessary data was extracted. Risk of bias and quality of studies were assessed by CASP and SYRCLE checklists.

Generally, therapies resulted in improvements in muscle strength and sialic acid levels. Aceneuramic acid initially showed promising results, but a well-conducted recent study concluded the association was insignificant. N-acetylmannosamine showed a significant decline in rate of muscle deterioration. Lower extremity strength significantly decreased in comparison to the placebo group ($p=0.006$). Also, a smaller decrease of Adult Myopathy Assessment Tool (AMAT) Total score compared to placebo showed a decrease in rate of muscle degeneration ($p=0.0453$).[2] Both aceneuramic acid and N-acetylmannosamine were well tolerated in patients and typically only mild GI side effects were experienced. Sialyllactose was found to be most effective at a high dose in mice, significantly increasing muscle size ($p<0.01$) and muscle force ($p<0.001$) to the same level as control littermates.[3]

Despite positive findings, the significance of substrate therapy still needs to be confirmed. Although aceneuramic acid's findings were insignificant, N-acetylmannosamine should continue to be investigated and promising results from Sialyllactose has potential to be explored in human clinical trials as GNEM continues to become better understood.

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In-sourcing of monoclonal antibodies (mAbs) and the impact on transportation in secondary care: A rapid review

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The use of monoclonal antibodies in healthcare has increased steadily over the years since their debut in the 1980's. Since then, they have become a mainstay treatment and have revolutionised the management of many chronic life-threatening diseases. However, compounding and transportation of these lifesaving medicines is currently carried out by pharmaceutical companies not the NHS. The upcoming Transforming Access to Medicines (TRAMS) scheme aims to in-source the preparation of specialty medicines including mAbs to new integrated facilities.[1] Meaning it's imperative that new appropriate guidelines are constructed detailing aspects of transportation, storage and manipulation after preparation at these facilities. This rapid review aims to undertake a systematic search of literature regarding transportation and storage of the prepared monoclonal antibodies Rituximab, Infliximab, Trastuzumab and their biosimilars.

Embase, Medline and Scopus were screened systematically for papers that investigated the stability of Rituximab, Infliximab, Trastuzumab or their biosimilars. After following a thorough 12-step duplicate removal process, papers were then removed based on inclusion/exclusion criteria and manual selection leaving 12

papers for critical appraisal. The methodology for this review followed a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach.

The literature review found stability of mAbs for up to 30 days or potentially longer when refrigerated at 2-8°C and protected from light. The methodologies from studies included were compared against the Specialist Pharmacy Service (SPS) guidelines for assessing stability of biopharmaceuticals to assess validity of results.[2]

This report recommends NHS Wales should conduct in-house research into the transportation of mAbs as this specific area of research is scarce of papers. If this research is conducted it would provide a solid foundation of data for the creation of mAb transportation guidelines which would allow the effective and efficient use of the new TRAMS integrated centres.

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The impact of OTC antibiotics on antibacterial resistance.

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Antimicrobial resistance (AMR) is one of the predicaments faced by healthcare today. AMR rates are rising due to multiple factors, one being the over-the-counter (OTC) availability of antibiotics.[1] Inappropriate use of antimicrobials clinically and OTC drives a higher mutation rate as selective pressure arises. Bacteria gain resistance or cross-resistance due to this use over time.[2] Neomycin is an OTC aminoglycoside. Its use is concerning as its OTC availability is thought to contribute towards AMR.[3] The aim of this project was to identify mutations associated with neomycin resistance in *Staphylococcus aureus*.

The ESKAPE pathogen *Staphylococcus aureus* was selected. Sensitive and resistant genomes were downloaded and compared from the NCBI database. Genes of known association with aminoglycoside resistance in *S. aureus* were identified from literature. An alignment tool (T-Coffee) was used to align gene sequences (4). Mutations were highlighted in sequences and genes of interest with high mutational frequency were further analysed.

Genes of known resistance to aminoglycosides were defined, mutational frequency between strains was recorded. Observation was that a higher mutational frequency was identified in genes associated with efflux pumps and limitation of drug uptake mechanisms. To confirm the presence of stable mutation, amino acid sequences of genes with high mutational frequency were analysed. Observation was that the same resistance mechanisms had a high amino acid mutation upon analysis.

Genes of particular interest (*menD, menE, sigB, pbp2A*) were discussed in further detail to determine the potential mechanism by which they contribute to AMR. Overall, although the mutations identified through analysis could play a significant role in neomycin resistance and could explain cross-resistances, bioinformatic techniques alone cannot fully identify mutations responsible for aminoglycoside resistance and cross-resistances. Further laboratory experiments should be used to identify correlation between point mutation and development of AMR in *S. aureus* to aminoglycosides.

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Y Gymraeg a'r MPharm: Archwiliad o brofiad myfyrwyr graddedig sydd wedi ymgymryd â darpariaeth Cymraeg y cwrs

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Mae dewis iaith yn hanfodol i rai cleifion ac yn cael effaith sylweddol ar safon y gofal a ddarperir.[1] Bu'n un o broblemau mwyaf arwyddocaol yng ngwasanaethau iechyd.[2] Yma yng Nghymru bu llawer eisiau cyfathrebu yn eu hiaith gyntaf trwy gyfnod o salwch er bod llawer yn rhugl yn y Gymraeg a'r Saesneg.[1,3] Mae ymdrech yng Nghymru i wneud 'Gynnig rhagweithiol' i gleifion drwy gyfarch yn ddwyieithog sy'n rhan o fframwaith 'Mwy na Geiriau.[4] Nod yr ymchwil yma yw archwilio barn a phrofiad myfyrwyr graddedig sydd wedi ymgymryd â darpariaeth Cymraeg ar lefel israddedig yr MPharm er mwyn darganfod parodrwydd i weithio'n ddwyieithog.

Cafodd ymchwiliad ansoddol ei weithredu oherwydd ei natur archwiliadol a disgrifiadol. Edrychwyd ar farn a phrofiad ein myfyrwyr graddedig a sut a pham bod y farn yma'n bodoli. Defnyddiwyd samplu bwriadol i gasglu ein cyfranogwyr i'r astudiaeth. Cyfwelwyd 7 cyfranogwr gan ddefnyddio cyfweliadau lled-strwythuredig dros y platfform 'Zoom'. Ar ôl derbyn caniatâd, cafodd y cyfweliadau eu recordio at ddibenion trawsgrifio a chafwyd eu dadansoddi yn thematig.

Canfuwyd 4 thema trwy ddadansoddi diddwythol ac anwythol. Bu elfennau ychwanegol yn dynodi elfennau ychwanegol gellir cynnwys a phwysleisio ar yr MPharm. Mae hyder/anhyder yn dynodi sut mae hyder yn effeithio defnydd yr iaith yn y gymdeithas. Bu effaith yr iaith yn dynodi sut mae dewis iaith yn effeithio ar ryngweithiadau a'r thema olaf yn manylu ar ddefnydd y Gymraeg yn y flwyddyn sylfaenol.

Rhagwelwyd o'r canlyniadau byddai cynyddu'r ddarpariaeth Cymraeg ar y MPharm yn fuddiol i gefnogi hyder, ymwybyddiaeth ac yn bwysicaf oll, cefnogi cleifion. Mae'r astudiaeth hon yn dod i'r casgliad bod hyder yn ffactor mawr wrth edrych ar ddefnydd yr iaith Gymraeg gan fyfyrwyr. Bu angen codi mwy o ymwybyddiaeth er mwyn cynyddu'r ddarpariaeth a'r ymarfer Cymraeg ar y cwrs a hynny yw, gwella parodrwydd i weithio yn ddwyieithog.

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Exosomes: Therapeutics of the Future or Overhyped?

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Exosomes are small extracellular vesicles that are produced inside endosomes and released to the extracellular space where they are involved in many physiological and pathophysiological processes.[1] Exosomes have been identified as potential future therapeutic options for multiple diseases such as cancer and cardiovascular disease due to their non-toxic and non-immunogenic properties.[2] The review aims to discover the current state of research on exosomes as drug delivery vectors and which diseases are being investigated.

Peer-reviewed literature were sourced through PubMed related to the therapeutic indications of exosomes and clinical trials were included from the ClinicalTrials.gov database. The search was focused to include English-language studies using exosomes as drug-delivery vectors to treat specific conditions or diseases. Review papers and studies using exosomes as diagnostic tools, or those studies outlining the isolation and manipulation techniques of exosomes were excluded. The search was then analysed to highlight trends in terms of publication date and diseases, cargo of the exosomes and origin.

The initial search yielded 494 studies using exosomes in many different diseases. Cancer was found to be the most abundantly researched disease with 120 studies, and exosomes were found to be effective carriers of

conventional and new treatments, such as for paclitaxel and doxorubicin. They significantly reduced the tumour size and systemic side effects of therapy. A total of 31 clinical trials were also found, 8 of which related to COVID-19-related conditions, indicating the rise in research into treatments for the recent pandemic.

Exosomes have been seen to have many advantages in the treatment of multiple diseases and therefore have a future potential as therapeutic agents. Exosome research is rapidly developing with new potential treatments for COVID-19 in clinical trials. This review indicates that more research needs to be done to develop exosome research from pre-clinical research to approved therapeutics.

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Alternative routes of delivery of vitamin B12: A rapid review

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Vitamin B12 deficiency has an estimated prevalence of 6% in adults in the UK and US, and rises to 20% in those over 60 years old.[1] Currently, vitamin B12 deficiency of dietary origin is treated with oral cyanocobalamin tablets. For patients with B12 deficiency of non-dietary origin, intramuscular injections of hydroxocobalamin is the first line treatment.[2] Pernicious anaemia is the most prevalent cause of B12 deficiency of non-dietary origin.[3] It is a result of a lack of a glycoprotein, Intrinsic factor (IF), which is essential for absorption of vitamin B12 in the ileum. Due to the absence of IF, oral tablets are ineffective in treating pernicious anaemia patients. Currently, the only alternative is intramuscular injection of hydroxocobalamin. This rapid review aims to assess published literature on alternative routes of delivery for patients with vitamin B12 deficiency, providing an assessment of the feasibility of alternative vitamin B12 products.

Medline and Embase databases were searched for relevant papers looking at nasal, sublingual, buccal and microneedle delivery. The results were extracted to EndNote and the inclusion criteria was applied. Following this, the included papers were critically appraised using either CASP or JBI checklists.

The initial search identified 501 publications. After applying the inclusion criteria, a total of 13 papers remained containing both pre-clinical and clinical data for nasal, buccal, sublingual and microneedle delivery of various forms of vitamin B12.

Due to different forms and doses of vitamin B12 used in the included papers, a direct comparison between studies could not be performed effectively. However, the pharmacokinetic data produced in the studies show sublingual, buccal, nasal and microneedles can delivery vitamin B12 effectively. Whilst future work is clearly needed to translate any new delivery method to the current treatment framework, sublingual, buccal, nasal and microneedle delivery all show promise for future therapies.

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Optimising the St. Mary's Pharmaceutical Unit (SMPU) standard operating procedure for the formulation of three-component oral rehydration powder

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Oral rehydration powder (ORP) formulated in the St. Mary's Pharmaceutical Unit (SMPU) comprises three constituent powders, each with varying particle sizes: sodium chloride, sodium bicarbonate and glucose. ORP is recommended as a first-line treatment to treat diarrhoeal disease.[1] Current SMPU formulation method is labour intensive, involving many steps. The study aims to explore and propose a more robust manufacturing method, whilst ensuring homogeneity of the powders during use to prevent segregation of powders.[2,3]

In this study, various formulation methods were tested by the following analysis methods. Particle size analysis were undertaken using laser diffraction to characterise the constituent powders. Scanning Electron Microscopy was used to gain a greater understanding of the morphology of the constituent powders with different particle sizes, which were fractionated using the sieves. A tap density test was run to determine the flowability of the powders. Lastly, quantitative assays were run on each ORP sample formulated to check the homogeneity of the powders. These five analysis methods evaluated the quality of the formulation.

Five out of six proposed formulations satisfied the homogeneity test. The findings show that whilst the current SMPU method provides adequate homogeneity of the powder, this can be further optimised by using a pestle and mortar to pre-process the powders for 5 minutes. A sieving step for the powders post-grinding was deemed unnecessary and so was eliminated.

The study generally supported the more efficient use of large multi-dose containers as an alternative packaging for the oral rehydration powders, rather than the use of single-dose containers. However, further investigation is required to determine the stability of the formulation and the potential risk of contamination.

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Exploring the views and experiences of informal carers on medicine support and management

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Informal carers are unpaid and are usually relatives or friends.[1] Contrastingly formal carers are paid and employed.[2] Formal carers can work in different types of settings such as care homes and domiciliary settings.[2] There is a lack of research into the perspectives of informal carers on supporting with people with their medicines. Therefore, this project aims to understand the views and experiences of informal carers on supporting the person they care for with their medicines.

Content analysis of medication policy documents for domiciliary care settings in Wales was conducted.[3] The purpose of doing this was to understand how formal carers support individuals with the safe and effective use of medicines and to inform the design of a topic guide to explore carers experiences of medicine support. Semi-structured interviews were conducted with informal carers over Zoom or by telephone.[3]

A total of 13 policy documents from seven health boards were analysed. Three interviews were conducted with informal carers. All the participants supported the person they care for with their medication. Three main themes were identified: nature of support, support from professionals and recommendations.

Carers support the person they care for with their medicines in various ways, ranging from prompting to physically administering the medication. The results show that supporting with medication can be difficult at times when the individual takes many medications all with different instructions. The results of this project provide more evidence for the importance of the Involved and Informed campaign.[4] These results should be considered when developing resources on medicines support and management for informal carers. To conclude, this research provides an insight into the experiences of informal carers supporting with medication. Future research should aim to explore the experiences of a larger number of informal carers in supporting with medicines.

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Investigation into tricyclic antidepressant-related polypharmacy overdoses in England and Wales from 2015 to 2020

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Tricyclic antidepressants (TCAs) are a class of antidepressants that are no longer the first line treatment for major depressive disorder (MDD) due to serious adverse reactions such as arrythmias.1 This study investigated the prescribing patterns of TCAs in England and Wales and the reported deaths involving tricyclic antidepressants from 2015 to 2020. It also established the common agent classes used alongside TCAs in those poisonings.

Accessed the United Kingdom Poisoning Information Database (UKPID) from the National Poisons Information Service (NPIS) for information on TCA-related poisonings. There were 2749 enquiries from 2015 to 2020, with 1661 TCA-related polypharmacy cases identified after removing duplicates and single agent TCA enquiries.

Approximately 99.5% of the prescribing data were from primary care in England and Wales with over 70% of the prescribing for amitriptyline. The Office of National Statistics (ONS) data showed an increase in TCA-related polypharmacy deaths by 2.7% from 2015 to 2020. In the UKPID data, 463 different agent classes were identified and categorised into 114 agent classes. The top two agent classes in the UKPID data were opioid analgesics (13.1%) and non-opioid analgesics (12.8%).

Despite TCAs recommended as the last resort for treating MDD, there is still high demand overall for TCAs especially for amitriptyline which continued to increase in the prescribing data by 19.3% by 2020. Analgesics are still a high-risk drug class for self-poisonings especially paracetamol despite packaging restrictions. Similar investigations into TCA-related poisonings, prescribing and deaths could be investigated in Scotland and Northern Ireland to compare findings across the UK.

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Evaluation of ASSIST-CKD, the kidney function surveillance programme aiming for early detection and improved treatment of patients with chronic kidney disease.

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Chronic Kidney Disease (CKD) is a condition that affects around 10% of the UK population.[1] CKD is a progressive disease with a variety of co-morbidities; however, patients can be asymptomatic until late in

disease progression. This project evaluates ASSIST-CKD, a kidney function surveillance programme which aims to identify patients at high risk of CKD allowing them to receive the benefits of early referral.

This project evaluates ASSIST-CKD in Swansea Bay and Hywel Dda University Health Boards at a patient-level with the analysis of anonymised patient data including demographics, blood test results etc. An analysis of patient's kidney function once referred to renal services was performed as well as a calculation of late referral rates. All data was handled within Excel.

Patients renal function was found to improve after referral to renal services by ASSIST-CKD halting disease progression. Sub-group analysis found a late referral rate of 4.3%. Prescribing data of co-morbidities highlighted the fact that many patients had co-morbidities that they were not being treated for until seen by secondary renal services.

ASSIST-CKD was found to be an effective tool in identifying patients at risk of CKD and halting their disease progression. Patients benefitted from the delay in needing renal replacement therapy or transplantation, and the disadvantages of late referrals including increased mortality and poor patient outcomes were avoided.

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The impact of at home infusion on patients: A rapid review

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Ambulatory care is the overall term for medical services given to those not admitted to hospital, also called outpatient care. An area of ambulatory care is ambulatory infusion, which is also known as home infusion. Home infusion can lower healthcare costs whilst also providing a higher standard of care for patients[1], and it is used for a variety of treatments. For example, analgesics, anaesthesia, cancer therapy, parenteral nutrition (PN) and antimicrobials. This review aims to assess the patient experience of using home infusion pumps to determine patient preferences and areas for improvement.

Three databases were searched: MEDLINE, EMCARE and PubMed to discover relevant studies. They were screened for eligibility and placed under full text review. After papers were identified, data was extracted and assessed for quality and bias.

11 studies are included in this review, results varied between studies but 3 key themes were identified: infusion pump use, pump design and home infusion services. Generally patients were satisfied with home infusion pumps[2] and they allowed patients to feel more free in the home environment[3], however patients lacked the individualized information to feel completely secure with using pumps at home[4].

The impact of home infusion on patients varies, however the importance of patient involvement, education and communication are essential for effective home infusion. Research is lacking regarding patient preference and further study into the practical, real life use of home infusion pumps is needed in order to develop the most effective use of home infusion pumps.

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A Rapid Review of the Test Methods Used to Analyse Dissolution of Dissolving Microneedle Delivery Systems

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Microneedle Array Patches (MAPs) are an emerging drug delivery system that physically disrupts the stratum corneum, using needles less than 1mm in length, to enhance drug delivery into and/or across the skin.[1] There are no standardised tests for these novel dosage forms. For a dissolving MAP (a sub-category of MAPs) dissolution tests will be key to the development of quality assured products[2], as dissolution is their principal mechanism of drug release.[3] The aim of this review is to identify, characterise and evaluate dissolution tests that have been used within the literature to examine dissolving MAPs for delivery of active pharmaceutical ingredients (API) to the skin.

The search terms 'dissolving' and 'microneedle', and variations of these terms, were used to conduct the literature search on four databases: Medline, Embase, Scopus and Web of Science. Studies were screened using Endnote for their eligibility based on specific inclusion and exclusion criteria that resulted in identification of studies published from 1998 that used a dissolution test to characterise a dissolving MAP for API delivery to the skin.

Forty-three studies were included in the review. Different apparatus were used and the most common parameters used in dissolution tests included: a phosphate buffer saline medium maintained at pH 7.4 and 37°C with agitation via stirring at 100 rpm, a 30 minute test duration, a 1ml sample volume and a HPLC assay method.

The results show that there is a variety of dissolution testing methods being used for MAPs. There are similarities to pharmacopoeial transdermal patch dissolution tests, but most researchers are not using tests to pharmacopoeial specification. Pharmacopoeial transdermal patch methods could be modified for MAPs by using smaller volumes and time intervals or increasing the number of MAPs. More research and harmonisation is required to determine a standard dissolution test for MAPs.

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Osteoblasts as regulators of prostate cancer cellular dormancy: a rapid review

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Prostate cancer (PCa) can resurface in bone long after seemingly successful treatment[1]. This is likely due to the ability of metastatic PCa cells to enter a dormant state in bone marrow[2]. Relatively little is known about the mechanisms which control cancer cell dormancy, however interactions with surrounding cells are important. Observations that PCa cells localise with osteoblasts[3], and the apparent role of osteoblasts in stem cell dormancy[4], have sparked interest in osteoblasts as potential PCa dormancy promoters. This review aims to determine whether osteoblasts promote PCa dormancy and, if so, how. This has the potential to improve our understanding of dormancy and help identify novel approaches to treatment.

Five databases were searched, for in vitro and/or in vivo studies evaluating the role of osteoblasts in PCa dormancy. Their suitability for inclusion was evaluated using pre-defined inclusion and exclusion criteria. Relevant data were extracted from each, and their quality assessed.

7 of the 144 records returned were included. These studies reported associations between osteoblast exposure and PCa dormancy characteristics, associations between osteoblast-associated signalling

molecules and PCa cell dormancy characteristics, and the proposed mechanisms of action behind the effects observed. Their collective data suggest osteoblasts can have antiproliferative effects on PCa cells in vitro. Whether this is associated with increased apoptosis or senescence is unclear. There is better evidence to suggest that some osteoblast-secreted factors induce PCa dormancy, primarily through regulation of Wnt/β-catenin and p38 mitogen-activated protein kinase signalling pathways.

Whilst there is insufficient evidence to show directly that osteoblasts promote PCa dormancy, there is a strong suggestion that certain osteoblast products can. These results confirm the relevance of this hypothesis. Further work should aim to better characterise the cellular state associated with osteoblast exposure, the impact of osteoblast differentiation, and confirm the production of these secreted factors by osteoblasts in humans.

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Does electronic prescribing reduce adverse drug events in hospitalised patients, and will it help to inform the medicines safety dashboard in Wales?

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Adverse drug events (ADEs) are a global health concern for hospitalised patients.[1] E-prescribing (EP), with clinical decision support systems (CDSS) have been suggested as a patient safety management tool, reducing medication errors and, therefore, ADEs.[2] This review gathers literature to assess the efficacy of e-prescribing on reducing ADEs, preventable ADEs and potential ADEs (pADEs) in hospitalised patients. Assessing whether e-prescribing aids the documentation of ADEs, informing the All Wales Therapeutic and Toxicology Centre (AWTTC), was a secondary objective.

Embase, Emcare, Medline, Scopus and Web of Science databases were searched identifying articles meeting the pre-determined inclusion criteria. Eligible studies assessed ADE incidence rates in hospitalised patients, or a comparison with a control/after EP implementation. Following the PRISMA flow diagram,[3] 38 articles were brought forward for full-text screening and 12 articles met the criteria. For the secondary objective 6 studies were screened using the full-text, but did not answer the objective, so were not included.

The 12 studies amassed 159,794 patients spanning 5 countries, across three study designs: 5 before-after, 1 case-control and 6 cohort studies. ADE detection was inconsistent across the studies. 5 out of 7 studies with a comparator showed a reduction in ADEs, with the other 2 studies showing a reduction in preventable ADEs with EP/CDSS. Studies assessing potential preventability using EP/CDSS, showed a significant proportion of ADEs could have been prevented.

Most studies showed an ADE reduction with EP/CDSS implementation, with a reduction of preventable ADEs also mainly seen. There were very mixed results in the rates of pADEs, with some significant increases and decreases. Further studies of EP/CDSS use in Wales would be extremely beneficial, but the international data for reduction of ADEs is promising for patient safety. Assessing the documentation of ADEs after EP/CDSS is an area for future research, as the data is currently unavailable.

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The effect of RyR2 mutation on channel Ca^{2+} sensitivity leading to CPVT, and evaluation of store overload-induced Ca^{2+} release hypothesis: a rapid review

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disease. It occurs in structurally normal hearts and is induced by stress/exercise; the exact molecular mechanism is not fully understood. Mutations in the cardiac ryanodine receptor (RyR2, controls Ca^{2+} release from SR) have been implicated in CPVT,[1,2] causing abnormalities in Ca^{2+} regulation. This review discusses the effect of CPVT mutations on RyR2 sensitivity to Ca^{2+} and whether sensing abnormalities occur in response to Ca^{2+} on the cytoplasmic or luminal side of the channel. It evaluates a proposed hypothesis for the molecular dysfunction of mutated RyR2 called store-overload induced Ca^{2+} release (SOICR).

Medline, Scopus and PubMed databases were used to search the empirical literature. Primary studies in English concerning RyR2 gain-of-function mutations were included. All studies assessed the effect of RyR2 mutation on channel Ca^{2+} sensitivity. A PRISMA flowchart was used to record data collection. A total of 14 studies assessed for quality satisfied the inclusion criteria. A narrative synthesis was used to synthesise the findings.

All of the included studies confirmed that mutations increase Ca^{2+} sensitivity, with the majority reporting enhanced luminal sensitivity, supporting SOICR. Only 4 CPVT mutations out of 16 were found to cause an increase in cytosolic sensitivity and many studies were unable to conclusively differentiate between the contribution of cytosolic vs luminal sensitisation due to limited experimental capacity. The RyR2 expression level was found to be comparable between WT and mutant with two exceptions where the mutant was expressed at lower levels. Two mutations required PKA to unmask dysfunction.

Enhanced Ca^{2+} sensitivity of RyR2 is a major factor of channel dysfunction in CPVT but other factors such as channel expression levels and phosphorylation must be considered. Further research is required for a full characterisation of CPVT mutations as they produce heterogenous effects therefore, it is impossible to conclude that one general mechanism can explain CPVT.

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Are Zinc Transporters Good Biological Targets for the Prevention of Metastatic Prostate Cancer: a rapid systematic literature review

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Prostate Carcinoma is the most common form of cancer in men across the UK with more than 47,500 cases being identified annually. At present, advanced prostate cancer (APC) is not curable and treatments are limited to hormone therapy alone or combinational chemotherapy with hormone therapy. The aim of this review is to critically appraise literature related to zinc transporters and their physiology in prostate cancer and determine potential targets for decreasing the progression of the disease.

Articles were extracted from four scientific databases; MedLine, Web of Science, Scopus and Embase in order to assess literature related to the SLC39A and SLC30A zinc transporters and gather information regarding

their role in the progression of prostate cancer and metastasis. Studies were screened for eligibility based on the PICO framework and inclusion/exclusion criteria. Studies selected for inclusion were analysed for potential bias and relevant key data was extracted and appraised.

In total, 9 publications were included in this systematic review based on the framework and eligibility criteria. This review complies data related to the role of zinc transporters in prostate cancer and the downstream effects elicited from the modification in expression of the various transporters, along with any alterations in transporter expression in relation to disease development and progression.

The physiological role of zinc transporters in prostate cancer is eminently diverse, with transporters displaying antagonistic functions in prostate cancer. The transporters; ZIP1, ZIP3, ZIP4 and ZnT7 were shown to produce anti-tumour properties, including the inhibition of cell proliferation, migration and invasion and induction of apoptosis. Per contra, the ZIP6, ZIP9 and ZnT4 transporters were associated with increased disease progression inducing epithelial-to-mesenchymal transition, migration factors and NF-kB signalling respectively.

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Available at: https://prostatecanceruk.org/prostate-information/just-diagnosed/advanced-prostate-cancer

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Evaluating puncture performance tests used for dissolvable microneedle array patches: a rapid review

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Microneedle array patch (MAP) is the term used to describe combination products that employ microneedle technology for transdermal or intradermal drug delivery.[1] MAPs present numerous advantages over other drug delivery systems; this technology can potentially eliminate the need for cold chain storage[2] and are painless and easy to self-administer.[3] However, there is no defined standardised test for the puncture performance of MAP technology to ensure safety and efficacy in patients.[4] An exploratory rapid review was conducted to identify and characterise puncture performance tests (PPTs) that exist in the published literature for dissolvable MAPs, to determine their potential for adoption or adaptation as a standardised PPT method.

A literature search of scientific peer-reviewed papers identified terms related to ‘microneedle’ and ‘dissolvable’ in the titles and abstracts of publications listed in four electronic databases: EMBASE, Ovid Medline, Scopus, and Web of Science. The eligibility of articles was assessed in two stages against pre-determined inclusion and exclusion criteria. The review was performed following the PRISMA protocol.

Sixty-one articles were identified for data extraction and synthesis. Two principal methods to quantify puncture performance were identified: visual identification and a count of the microchannels (95%) and measurement of trans-epidermal water loss (TEWL) (5%). A diversity of skin models, apparatus, and test conditions have been used in PPTs to evaluate puncture efficiency.

This review has identified visual identification, followed by a count of microchannels, as the most common PPT method and this has the potential to become a standardised PPT. However, this PPT method needs to be developed with universally accepted test conditions, apparatus, and skin models. Further research should develop a synthetic skin model with representative mechanical properties.

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Preterm Birth Prevention: Opportunity for Biological Therapeutics

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Preterm birth is defined as the birth of an infant before 37 completed weeks gestation.[1] It is the leading cause of neonatal morbidity and mortality globally with an estimated 15 million preterm births occurring each year, with more than 1 in 10 infants being born premature.[2] There is a scarcity of therapeutic options available. Biologics are medicines produced or derived from biological sources; and have complex variable structures. They can be more selective with reduced side effects. This review aimed to identify biological therapeutics currently being used in the treatment of preterm births and to investigate the pre-clinical landscape for potential new biological therapeutics.

Four databases were searched; PubMed, Medline, Embase and Cochrane Library, for English language studies investigating preterm birth therapeutics. Studies were extracted into EndNote 20, duplicates removed, studies screened, and data extracted. A PRISMA flow diagram was used to record the number of results through each phase of data collection.

Of the 2799 articles initially identified, 131 were included in this review. Twenty different therapeutic strategies were identified, 2 being licenced and available on the market, and 18 therapeutics under pre-clinical investigation. These 20 therapeutic areas could be split into therapies that target uterine contractility, therapies that maintain a natural microorganism population, and therapies that target inflammation; all of which are major contributors to preterm birth.

Much of the studies identified in the pre-clinical landscape are in their infancy with limited research. Some are more advanced with better quality evidence, such as probiotics and interleukin-1 receptor antagonists; and some are very much future ideas such as recombinant interleukin-10. This review also identified antimicrobial peptides that could be exploited; but again, it is vitally important that research and funding be greatly increased if treatment wants to progress to reduce preterm birth rates in the future.

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The Participant Perspective in Clinical Trials- How and When is it Captured? A Rapid Systematic Review

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Owing to the nature of neurodegenerative diseases, there has been a shift towards increasingly complex trials.[1] These can be potentially burdensome and difficult to design. For future clinical trials it's important that we acknowledge what participants experiences are, so that we can make improvements. Looking at their experience across all clinical trials is important, as issues will only be amplified. The aim is to look at; the method of perspective collection, what data is collected and when it relates to. Enabling us to identify common themes that arise between literature.

Five electronic databases were screened; Medline, Embase, PubMed, Scopus, and Web of Science to gather all literature relating to the perspectives of participants during clinical trials involving Parkinson's disease, Huntington's disease, and Multiple Sclerosis. Inclusion and exclusion criteria were applied. Eligible studies underwent analysis and a quality assessment. Interviews conducted by the LEARN (Listening to the Experience of participants in Neurosurgical trials) team were thematically analysed to contextualise our findings.

This review considers data from ten studies which met the eligibility criteria. 50% of papers captured perspectives by the means of questionnaires, subsequently a further 30% utilised interviews. All studies captured data relating to pre-trial elements with two papers also containing limited data regarding post trial. Key elements were recruitment and the informed consent process.

There's a gap surrounding when and how data is collected. It's apparent that to implement capturing perspectives to the degree desired is to incorporate patient perspective into the criteria of a trial. There's value in the depth of information that can be gathered, as it allows an understanding to be established facilitating the advancement in research. Questionnaires offer limited value as the data requires interpretation. The LEARN interviews provided insight into the depth of information that could be captured throughout the trial through semi-structured interviews.

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The impact of greenspace on mental health in urban areas: a rapid review

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Living in urban areas has been documented to have detrimental effects on mental health.[1] As urbanisation is set to rise[2], and mental illness is a growing concern[3], there is need for research to determine measures which may protect mental wellbeing in these settings. This review aims to determine what impact greenspaces have on mental health in urban areas. Additionally, to determine whether this relationship is affected by socioeconomic status and/or degree of urbanisation.

Three databases were utilised; Medline, Embase, and APAPsychInfo to collect articles investigating greenspace and mental health. Relevant studies were stored in EndNote[4] and screened against eligibility criteria. Once the final studies were identified, quality assessment was undertaken followed by data extraction.

Greenspace was found to have a beneficial effect on mental health in 78% of included studies. Greenspace near residential homes (within 100m) were found to be the most influential. When stratifying based on socioeconomic status, a modifying effect was seen with a greater beneficial effect on low socioeconomic groups in 64% of included studies. Contradictory, an increase in greenspace was seen to worsen mental health for more disadvantaged populations in two studies, but only when the greenspace area was perceived as 'unsafe' or 'unattractive'. Two out of three studies found a greater effect of greenspace in more urbanised areas however due to the small sample more research is needed to confirm this observation.

In conclusion, greenspace has the potential to act as a protective measure of mental wellbeing in urban areas, particularly for those in more disadvantaged neighbourhoods. However, before any benefit can be seen, greenspaces need to be of an acceptable quality and safety otherwise they may be detrimental to mental health. This has the possibility to influence implementation of greenspaces in future urban planning.

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Synthesis of a novel Phosphocysteamine prodrug to improve patient compliance in the treatment of cystinosis

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Cystinosis is a rare disease caused by a mutation in the CTNS gene.[1] This results in defective transporters, causing intra-lysosomal cystine levels to increase leading to the formation of cystine crystals all over the body. This mainly affects the kidneys, which leads to end stage renal disease and death[1]. Cystinosis is not just limited

to the kidneys but can affect many other organs all over the body.[2] The only approved treatment for all 3 types of cystinosis is an orphan cystine depleting agents called cysteamine.[3] However, cysteamine treatment compliance is greatly affected due to its unwanted side effects especially poor breath and sweat odours. Therefore, our research aims to synthesis a novel phosphocysteamine prodrug to overcome the side effects which hinder good compliance in cysteamine therapy.

We aim to do this by exploiting the formation of a P-S bond under various reaction conditions. Initially for this we protected the amino group of the cysteamine using di tert-butyl-dicarbonate to synthesis Boc-cysteamine. This molecule was then used to react with various phosphate compounds under various conditions to synthesis our desired phosphocysteamine prodrug with a phosphorothioate (P-S) structure.

All, but one reaction condition was unsuccessful in our synthesis attempts. The successful reaction, which exploited the redox reaction of phosphite with $TeCl_4$, was limited due to its low yield (5.36%, 158mg) and lack of further characterisation of the synthesised molecule via ^{13}C NMR and melting point analysis.

This means that overall, we were unsuccessful in reaching our desired aim despite seven attempts to synthesis a phosphocysteamine prodrug. Therefore, there is a vital need for further research to be done to obtain a reliable, high yielding method for the synthesis of a phosphocysteamine derivative which can then be further tested or even be used as an intermediate to synthesis a more active cysteamine prodrug.

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The effect of pleiotropic changes on antimicrobial resistance in bacteria: a rapid systematic review

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Pleiotropy is the phenomena in which changes in a single gene contribute to multiple, distinct and apparently unrelated phenotypic traits.[1] These alterations are vital for bacterial survival when confronted with antimicrobial stress – a mutation in an effector gene can grant increases in virulence, as well as rapid and ambiguous development of antimicrobial resistance.[2] Antimicrobial resistant bacteria already cost the NHS approximately £180 million per year.[3] The aims of this review were to collate and compare publications regarding bacterial pleiotropic modifications to draw conclusions on overall benefit, and to establish whether more research needs to be conducted to improve targeted antimicrobial therapy.

Scopus, Embase and PubMed were searched from January 2000 to November 2020. English publications were eligible only if the bacteria in the study went through pleiotropic changes, with these alterations having to alter antimicrobial resistance. Titles and abstracts were initially screened using an eligibility criterion - all relevant papers were then subjected to a full text review and critical appraisal, with key data extracted and analysed.

Of the 569 papers returned from the searches, twenty were included in the review. Due to the difference in the publications, a meta-analysis could not be performed. This review evaluated and compared the following: greatest MIC increase and decrease, resistance mechanisms, morphology changes, bacteria used, antimicrobials used, Gram of bacteria and intervention applied.

Despite associated fitness costs, pleiotropic alterations are extremely beneficial to bacterial survival via rapid development of a vast array of resistance mechanisms. This was displayed in the average greatest MIC increase of 261.6-fold, whereas the average MIC fold decrease was only 41-fold. Further research should be conducted into pleiotropic bacteria - opening the door to novel and commercially available antimicrobial treatments as well diagnosis techniques. This would be an exciting development in antimicrobial stewardship, greatly reducing the threat of multi-drug resistant bacteria.

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Exploring the preparedness of MPharm IV students at Cardiff University for the Oriel process and foundation year training

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Due to the COVID-19 pandemic, students for the academic year of 2021-22 undertook the majority of their degree online.[1] Additionally, the MMI (Multiple Mini Interview) exam was removed from the Oriel process for applying for foundation year posts.[2] Therefore, students' preparedness for Oriel and foundation year training may have been impacted. The aim of this study was to explore the preparedness of MPharm IV students at Cardiff University for Oriel and foundation year, considering the effects of the pandemic and online learning. Subsequently, suggestions would be made for future students to enhance their education and professional practice.

Following approval from the school's ethics committee, current fourth year MPharm students at Cardiff University were invited to participate via email. One-to-one, semi-structured interviews using Zoom were recorded (with consent), transcribed and anonymised. Transcripts were manually coded and thematic analysis identified common themes.[3] This was done deductively and an inductive approach was used but not needed.[4]

Thirteen interviews were conducted. Major themes that were identified were Oriel, foundation year, online learning and online exams. The Oriel theme explored the Situational Judgment Test (SJT) and numeracy assessments and the impact of placements, the school and Oriel on preparedness. The foundation year theme included the impact of MPharm teaching and placements on preparedness. The online learning theme covered the format and effects. Finally, the online exams theme included logistics and impact on future practice.

The findings from this study are not generalisable, but have allowed valuable insight into the preparedness of MPharm students for Oriel and foundation year. The research also allowed students to share how their preparedness has been impacted by online learning, in addition to general feelings surrounding the online format. Finally, it allowed for suggestions to the school and other stakeholders to help increase preparedness for future students.

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The Challenges of Tuberculosis Vaccinations in Preventing Infection; A Rapid Systematic Literature Review

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Tuberculosis (TB) infections are on the rise with Bacillus Calmette-Guerin (BCG) remaining to be the only vaccine used to vaccinate against TB. With the emergence of drug resistance against existing TB treatments, therapy against TB infection is limited and the need for new vaccines is coming of increasing importance).1 This systematic review aims to determine whether research from 2011-2021 has shown any potential novel TB vaccine candidates, whether they can be administered using different drug delivery methods to provide a treatment against pulmonary TB and whether they warrant further research.

Three bibliographical databases were used; PubMed, Medline (Ovid) and Scopus in order to find literature evidence of novel vaccine candidates, the existing BCG vaccine and different methods of drug delivery. Studies were screened for their eligibility based on specific inclusion and exclusion criteria which is displayed on a PRISMA chart. After reading the relevant included studies, they were subjected to a quality assessment using the CASP framework before the data from the included studies were extracted.

A total of 25 studies were included in this systematic review. This review summarises; the method of action of novel TB vaccine candidates and their effectiveness in comparison to the existing BCG vaccine. Furthermore, administration of the vaccines using different drug delivery methods to protect against pulmonary TB is discussed.

The most promising vaccine candidate was MVA85A, a recombinant viral vector vaccine inducing antigen specific cellular responses to protect against TB.2 Direct pulmonary delivery of vaccines via an aerosol has been found to be a promising method of vaccine delivery however it causes localised inflammation. However, a large proportion of the studies were carried out on animals so further studies need to be conducted to investigate the immunological responses of the vaccine on humans.

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Nanoparticles targeting breast cancer: Time to deliver?

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Breast cancer has recently become the most diagnosed cancer in the world with a high incidence to mortality ratio[1] proving to be a problem in developed and developing countries. Current therapies allow for the treatment of many forms of breast cancer but present their own drawbacks regarding the patient.[3] Innovative therapies including nanoparticles provide a means for targeted therapy for breast cancer and possibly averting the drawbacks experienced today.[2]

Four databases were searched for literature related to nanoparticles targeting breast cancer using a search algorithm and screened for relevant studies. Data was extracted on the material, therapeutic encapsulated, target ligand and targeted receptors from each study. A clinical trials register was also searched for relevant literature using a search algorithm and data extraction was carried out on the trials.

The results showed that most nanoparticles were lipid and polymeric and most studies encapsulated doxorubicin, alkaloid, and siRNA as a therapeutic, using a range of ligands targeting folate receptors, EGFR/ HER2 receptors and CD44 receptors present on breast cancer cells. Only one clinical trial was found to focus on the use of targeted nanoparticles for the therapy of breast cancer.

Pre-clinical studies showed great promise with increased efficacy compared to free drug, but this did not translate to clinical trials as most appeared to be trialling a combination therapy of previously approved nanomedicine with other small molecule anti-cancer therapies. Despite positive outcomes in pre-clinical studies, the prospect for targeted nanoparticle therapies for the treatment of breast cancer remains uncertain with limited human data and little formulations making it to clinical trials, let alone the drug market. Future implications could involve the development of more humanized mouse models to facilitate optimization of targeted nanoparticles targeting breast cancer.

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A rapid review of special medicine evaluations: patient experience

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Special medicines are unlicensed and therefore do not go through the same rigorous testing procedures as licensed medicines, consequently there is limited data available on their safety, quality, and efficacy[1]. Considering the increased risks associated with special medicines use, little is known about patient experiences using these medicines. This rapid review aims to create a question bank that can be used by specials manufacturers to help improve the services that they provide to patients. Research was completed in collaboration with a specials manufacturer, St Mary's Pharmaceutical Unit (SMPU).

Literature searches were conducted in four databases: Web of Science, Scopus, Medline and EMBASE via Ovid and articles were screened according to specified inclusion and exclusion criteria. The screening process employed has be shown using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram[2]. Relevant data was extracted from the included studies relating to patient issues/concerns with special medicines use and a thematic analysis was performed to provide a focus for the generation of the question bank.

Four studies were included as part of the data synthesis of this review. Two main themes were identified from the data analysis: a gap in patient knowledge and safety concerns. The questions used in the included studies were also evaluated to aid development of the question bank.

Proposed questions explored patients' understanding of special medicines, the provision of a written information leaflet and patients' knowledge surrounding the Medicines and Healthcare products Regulatory Agency's (MHRA) Yellow Card scheme. Further studies are required to expand the question bank as limited questions were created due to very few studies meeting the criteria outlined in this review.

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Development of an indirect sandwich ELISA for the quantification of Complement Factor H (CFH) – Thrombin (FIIa) complexes in human plasma in the context of psychosis

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Psychosis spectrum disorders are neuropsychological conditions which cause their sufferers to experience an altered perception of reality, causing considerable disability.[1] Emerging evidence points to a role of complement and coagulation in the development and progression of psychosis.[2] Both complement and coagulation systems are humoral protein cascades, which nominally form part of host defence and homeostasis (2). Previous work has shown that complement Factor H (CFH), a regulatory protein preventing excessive complement activation and Thrombin (FIIa), the central effector enzyme of the common coagulation pathway form complexes, which enhance the pro and anti-coagulatory activities of Thrombin.[3] Both complement factor H and Prothrombin (the inactive precursor to Thrombin) have been shown to be upregulated in those who have developed or are at high risk of developing psychosis. We hypothesise that concentrations of CFH-FIIa complexes would be higher in this cohort than the general population. This work aimed to develop and optimise an indirect sandwich format enzyme-linked immunosorbent assay (ELISA) that can measure CFH-FIIa complexes in human plasma, as no commercial ELISAs for this interaction exist.

An indirect sandwich ELISA for CFH was developed and by optimising antibody coating concentrations, blocking agent and concentration, sample concentrations, and detection antibody concentrations, we were able to measure FH in normal human plasma. This was then adapted into a CFH-FIIa ELISA, which was further optimised by adjusting coating antibody concentrations, sample concentration and incubation method, and

detection antibody concentrations. This ELISA was then compared with existing separate commercial CFH and Thrombin-Antithrombin ELISAs.

We were able to qualitatively measure CFH-FIIa complexes in human plasma spiked with Thrombin, however our ELISA did not compare favourably with related commercial ELISAs. Further optimisation and standardisation is required in order to accurately measure CFH-FIIa in human plasma, and in order to develop a mature commercial, diagnostic product.

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The following abstracts have been withheld as they have been or will be published elsewhere, and/or due to intellectual property or confidentiality issues:

Development and evaluation of candidate gabapentin buccal formulations for the treatment of burning mouth syndrome

Mercy Adeyemi1. A Sully2. H Davies[2] and JC Birchall1.
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An investigation into the impact of electronic prescribing and medicines administration (EPMA) on the provision of renal care in Wales by exploring the perceptions of healthcare staff

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Introduction of EPMA in South West Wales Renal Units: Exploring Patient Perceptions on the Impact on Their Care and Wider Life

Hana Akhtar and EM Mantzourani
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How polyphenols can act as anti-inflammatory agents: a rapid systematic review

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Role of bacterial adhesion in biofilm formation and how material properties influence this process

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Biomaterials in dentistry: The effects of surface and material properties on bacterial adhesion

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Antimicrobial Coatings In Orthopedics: Effect Of Material Properties On Bacterial Adhesion.

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Vestigial- Like Family Members VGLL1 and VGLL3 in resistance and its progression in cancer

Aaisha Begum and JMW Gee
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Do pomegranate extracts have potential to treat wounds? A rapid systematic literature review

Abigail Fong, V Celiksoy and C Heard
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Evaluating the clinical efficacy of contact lenses drug delivery of timolol to treat Glaucoma: A rapid systematic literature review.

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Exploring the Choose Pharmacy platform: The Independent Prescribing Service

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Evaluating the Independent Prescribing Service (IPS) in Welsh Community Pharmacies: A secondary data analysis

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Investigating the mechanistic function of the LAG-3 protein using computational approaches

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The role and potential therapeutic opportunity of lipids in the viral maturation of Zika Virus

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Exploring the use of microneedles to improve the delivery of parathyroid hormone for the treatment of osteoporosis: A rapid review of the literature

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A Characterising the make of bovine Lactoferrin (bLf) in lung cells

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Synthesis of novel compounds as potential LAG-3 targeting cancer immunotherapy agents

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Probing the nature of enhanced antimicrobial activity of polyphenols with metal ions

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Staff's perceptions on Electronic Prescribing and Medicine Administration (EPMA) in renal dialysis units: A qualitative study.

Ffion Haf Rees and EM Mantzourani.
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Targeting steroid sulfatase (STS) for breast cancer therapeutics

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Do Vestigial-Like (VGLL) Family Member proteins contribute to either breast or reproductive cancers?

Morgan Stark and JMW Gee
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Analysis of the association between plasma complement factor H concentrations and clinical assessments in hospitalised patients with sepsis.

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The synthesis of novel small molecule inhibitors targeting LAG-3, derived from an established hit molecule, as a potential cancer immunotherapy

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MSc Abstracts

Clinical Trial Disclosure: A Regulator's Nightmare

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Clinical trial disclosure was coined over 20 years ago to ensure the rights and safety of trial participants and to promote scientific advancement. Failing to register clinical trial protocols and tabular results disclosures leaves research gaps and represents one of the greatest threats to patient safety in clinical research. In 2007, the Food and Drug Administration Amendments Act 801 (FDAAA 801) was published in the United States and required sponsors to submit tabular results postings to ClinicalTrials.Gov within 1 year of the primary completion date. 10 years later, the Final Rule was published which clarified gaps in the FDAAA 801 and furthered the requirements for clinical trial disclosure. In this project, I aimed to assess trends in protocol registrations, tabular results postings, and the possible impact of the COVID-19 pandemic.

Using the advanced search feature in ClinicalTrials.Gov, I downloaded all available data for applicable clinical trials (ACTs) from 2000 to 2020. Analysis was performed on data extracted from ClinicalTrials.Gov on 01 March 2021. Clinical trials that were not applicable under the regulations were excluded for compliance calculations, whilst all trials were used for global trends. A trial was considered compliant if the protocol registration was submitted within 21 days of the trial start date and the tabular results disclosure was first submitted within 1 year of the primary completion date (FDA, 2016). I assessed global disclosure trends, trends in protocol registrations and tabular results disclosure, impact of the COVID-19 pandemic on disclosures, and possible ways in which compliance could be improved.

Of the 20,749 clinical trials identified in my research, 14,999 (72.29%; 95% confidence interval [CI]: 59.41 – 85.20%) had an associated tabular results disclosure. Of these trials, 1,330 (6.41%; 95% CI: 4.41 – 8.21%) were FDAAA 801 compliant. 197 out of 754 (26.13%; 95% CI: 4.16 – 48.09%) of the ACTs with a start date on or after 18 January 2017 were Final Rule compliant. Regulatory compliance continues to increase year on year slowly with numerical increases in the percentage of ACTs with an associated tabular results disclosure within 1 year of the primary completion date. The median delay from protocol registration to trial start date decreased from over 2500 days in 2000 to -30 days in 2020, 51 days less than the regulatory requirement and 30 days less than the International Committee of Medical Journal Editors requirement. The median delay from primary completion date to results first posted date decreased form over 1400 days in 2008 to 237 days in 2020, 128 days less than the FDAAA 801 requirement. COVID-19 ACTs in 2020 typically had delayed protocol registration and significantly early tabular results disclosure when compared to all ACTs.

The percentage of study records with an associated tabular results disclosure is high; however, compliance with FDAAA 801 and Final Rule is low. Compliance has increased following the FDAAA 801 and Final Rule but not to acceptable levels. The COVID-19 pandemic has had a positive impact on results disclosures, most likely due to increased public interest in clinical trial reports for this indication. Only time will tell if positive trends will continue moving forward. Compliance with regulatory deadlines will most likely not improve significantly until the Food and Drug Administration begin monitoring compliance internally, informing sponsors of their overdue trials, and enforcing financial sanctions. Until then, organisations such as the International Committee of Medical Journal Editors could join forces with public compliance groups to help promote regulatory compliance.

A rapid systematic review on the potential issue of biocides over-usage and the consequent development of antimicrobial resistance

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Overview: According to the Health and Safety Executive website, biocides are "used to protect people and animals from germs, to preserve manufactured goods, to protect industrial processes and to stop pests" (HSE, 2021). Biocidal products have a wide array of applications, especially preservatives and disinfectants. One of the desired properties of biocides is broad-spectrum antimicrobial activity, although there are drastic differences in efficacy levels between biocides (Augustin et al. 2004). Non-toxicity for the end user is another

key characteristic. Thus, it is of utmost importance to select the correct biocide according to the intended application.

Normally, bacteria colonise a surface in a format better known as a biofilm, representing a real challenge for biocidal efficacy. Biofilms are cause for concern, as more than 60% of infections are biofilm-driven (Hentzer et al. 2003). As they are a physical barrier, they reduce biocidal access to the cell. They will increasingly become ineffective and will possibly lead to antimicrobial resistance (Augustin et al. 2004).

The introduction of biocidal products within consumer products has exacerbated the issue of antimicrobial resistance and has led to the development of disinfectant resistance (Mc Carlie et al. 2020). While extensive studies have identified the mechanism of development behind the rising of antimicrobial resistance, including multi-drug resistance drugs, there is a lack of knowledge on the potential of a given biocidal agent to trigger antibiotic resistance (Mc Carlie et al. 2020; Kampf, G. 2018).

Aim of the systematic review: The aim of this rapid systematic review is to mine the literature for evidence of prolonged exposure to biocides at sub-lethal concentrations causing multidrug resistance or increased susceptibility to the biocidal product used.

Method and results: Scopus, PubMed and Web of Science have been employed; keywords have been used to further mine the findings and the publications were classified in relation to their year of publication, the industrial field they best described, if they were reviews and how relevant they were to the scope of this review. In total, 14 papers have been included in the last stage of this analytical review and their content has been mined for the following: have QAC been employed for the study (85.71), were biofilm-forming bacteria considered (50%), was there a significant increase in antibiotics and/or biocide resistance (14.29%), was the biocide in formulation (57%).

In conclusion, only two publications (14.29%) confirmed that the biocide tested significantly triggered MDR. However, in 57% of the publications, biocides were considered when in formulations as they are included in consumer products. When in formulation, other components play a role in enhancing their effect, thereby achieving a greater kill than simple biocides. Thus, biocidal products are able to effectively eliminate pathogens and contain infections.

Is there a role for Focal Adhesion Kinase (FAK) in acquired endocrine resistance in breast cancer?

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Up to 40% of breast cancer patients develop resistance to endocrine therapy. FAK upregulation has been observed in breast cancer and is associated with invasion and migration. Consequently this study aims to evaluate a role for FAK in the development of resistance. Three databases were searched, ninety papers evaluated and five accepted in a rapid review study. Endocrine resistant cell models (Tamoxifen resistant TAM-R and Faslodex resistant FAS-R) were generated. Western blot analysis and immunofluorescence evaluates the expression, activity and localisation of FAK and associated adhesion and survival molecules. The literature reveals no changes in total FAK expression. FAK activation is related to Src activity which is upregulated in resistance. FAK phosphorylation is sustained in TAM-R cells with an increase at sites Y861, Y925 and Y397. Western blot analyses backed up by bioinformatics data shows a decrease in total FAK in FAS-R cells and an increase in AKT activity in TAM-R cells. Survival analysis shows FAK expression is related to a decrease in relapse free survival. Differing patterns of FAK phosphorylation contribute to development of an invasive and migratory phenotype in TAM-R cells and upregulated AKT signalling may confer cell survival. FAK involvement in Faslodex resistance remain largely unclear.

Service Evaluation of Informed Consent Documentation at the Paediatric Oncology / Haematology Unit, Cardiff

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A Service evaluation was conducted to review the documenting of the Informed Consent Process with regards to clinical trial participation within the Paediatric Oncology / Haematology Unit at the Noah's Ark Children's Hospital for Wales, Cardiff. The evaluation reviewed the informed consent forms, consent label and the written documentation of informed consent in the clinical notes of 30 patients over a 3-year period. The service evaluation found informed consent form completion to be at a good level overall however, an issue with minor patient (those <16 years of age in Wales) engagement in the consent process was evident. Consent label completion and accuracy and the level and detail of physical documentation in the clinical notes was poor. None of the consent labels were completed in full and the majority of written documentation when present was of a basic level. There were, however, two examples of good practice, one involving the use of the consent label as an aid to reinforce the informed consent conversation and documentation and another exemplary example of detailed written documentation of informed consent both pre-consent and on the day of consent. The main recommendations of the service evaluation were that all existing and new members of the research team attend formal Informed Consent training with refresher training every two years and that the Research Nurse should have a more involved role in the consent process. A policy of 'check and confirm' should be introduced by the research support team to ensure all elements of the informed consent form are completed accurately before patients are registered to trial and that a revised version of the consent label should remain in use as the main form of documenting consent and that a further evaluation to assess completion levels should be conducted in the future.

Exploring the role of PYK2 in breast cancer subtypes

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Breast cancer is the most diagnosed cancer among women. The focal adhesion kinase PYK2 may sustain cancer enhancing signaling. Therefore, this study aims to explore it's role among breast cancer subtypes to further understand the mechanisms which govern these characteristics.

Here we discuss literature evidence suggesting prominent roles for PYK2 among breast cancer subtypes. We then investigated these via western blot and immunofluorescence studies to observe protein levels and subcellular localisation. Using bioinformatic/proteomic databases we distinguished correlations between PTK2B expression and patient outcome while highlighting key signaling pathways and known/predicted protein-protein interactions. We found that phosphorylation of PYK2 (Y402) resulted in signaling via the PI3K/AKT and MAPK pathways in all breast cancer cell lines and key signaling intermediates such as Src, p-Pyk2, MAPK, P130Cas, p-P130Cas and AKT were specifically enriched in the aggressive TNBC subtype. Immunofluorescence revealed that PYK2 colocalizes with vinculin and downregulates epithelial markers thus, facilitating EMT. Finally, we showed that increased PTK2B expression correlates with poorer patient outcome.

This research presents evidence of multiple roles for PYK2 across breast cancer subtypes and lays foundations for future research which could aid in developing novel therapies to target multiple aspects of PYK2 signaling simultaneously, thus, tackling breast cancer burden.

Evaluation of a Respiratory Physiology lead GP Direct Access Pulmonary Service at an NHS District General Hospital in the East of England

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Aims: This critical analysis aimed to fully evaluate the GP direct access respiratory physiology lead respiratory assessment service which has been conducted at Hinchingbrooke Hospital in Huntingdon Cambridgeshire since late 2010. The service was originally set up to allow General Practitioners in primary care to refer directly to the secondary care Respiratory Physiology department so that high quality diagnostic lung function and spirometry evaluations could be conducted.

Since the GP direct access pulmonary service (DAPS) started in late 2010 a dataset has been populated by the respiratory physiology team. This dataset was reviewed in detail using a descriptive analysis looking at how the service is used, patient demographics, outcomes, and accuracy of reporting of physiologist compared to chest consultants. This database currently stands at 973 patients referred in from 53 primary care GP practices across the local area which includes 9 full years of data 2011 – 2019 and partial data for 2010 and 2020. (Due to the Coronavirus-19 Pandemic unfortunately the service had to be put on hold during the majority of 2020 and the start of 2021).

This analysis showed that from 2011 to 2019 only 22% of all referrals to the GP Direct Access Pulmonary Service were recommended to be referred to the consultant chest clinic after respiratory physiologist assessment. Conversely a massive 64.6% of patients were referred back to be looked after in primary care. If this service did not exist, the effect on capacity for secondary care chest clinics would be significantly reduced.

The dataset consists of 973 patients referred from 53 GP practices since part way through 2010 to part way through 2020. 2011 to 2019 full years. Referrals have gone from 54 per year to 230 per year. 47% of referrals are male, 53% female. The Average age of patients is 60.3 years with a range of 18 to 95. Over the last full two years (2018 & 2019) the average age dropped to 55.7. The average BMI of patients referred is 29.4 with a range of 14.4 to 60.1. Smoking status of patients referred is 55.54% are ex-smokers, 25.91% are current smokers and 29.54 are never smokers. Currently the average waiting time from referral to pulmonary function tests is 29 days but this is gradually increasing as more people are being referred.

64.6% of patients are recommended to be cared for in primary care. 22% of patients are recommended to have a secondary care chest consultant referral. Diagnosis after pulmonary function tests is that 30% are normal, 20% are COPD, 18% Asthma, 9% COPD with an element of Asthma and 4% a restrictive pattern. There is excellent consensus agreement in diagnosis between Respiratory Physiologists and chest consultants. The service has excellent possibilities for being a high quality, excellent independent service with opportunity to develop further with the right support and training.

The GP Direct Access Pulmonary Service is an excellent service that has developed over the last 10 years. It is a great asset to primary care, secondary care and the patients it serves. With the right input it can further develop and provide a cost effective but very importantly Quality assured excellent service to this Hospital (Hinchingbrooke) but with collaboration with the CCG and other secondary care Trusts could be the way forward to deliver a world class pulmonary assessment service.

Exploring the Role of Pyk2 in Breast Cancer Subtypes

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Therapeutic resistance accounts for 90% of all cancer-related deaths and there is an urgent need to identify new targets to overcome this phenomenon.

This project aimed to identify if the Vestigial-like coactivator family members, VGLL1 or VGLL3, contribute to therapeutic resistance.

A rapid review was performed to identify publications that explored the association between VGLL1 or VGLL3 and anti-cancer resistance. Their protein and mRNA expression were explored in resistant breast cancer cell

lines using western blotting, immunofluorescence, microarray data and bioinformatics software, and versus clinicopathology.

VGLL1 and VGLL3 mRNA were elevated in acquired endocrine resistant breast cancer cell lines and VGLL1 negatively correlated to ER and prognosis. Literature supported this by reporting VGLL1 was often involved in driving cancer features and resistance mechanisms, whereas VGLL3's oncogenic nature was more tumour type-dependent. Protein expression did not correlate to mRNA profiles, but VGLL1 and VGLL3 nuclear co-expression with their transcription factor implied they signalled in resistant cell lines.

VGLL1 has the potential to be a driver of endocrine resistance in breast cancer whereas VGLL3's contribution to anti-cancer resistance needs to be further validated. Future studies should explore in vitro and in vivo whether VGLL1 can be targeted to treat cancer resistance.

Pharmacoeconomics of PD-1 & PD-L1 inhibitors: A rapid review of NICE recommendations

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The PD-1/PD-L1 immune pathway is the target of a novel class of drugs known as PD-1/PD-L1 inhibitors. By inhibiting this pathway, these therapeutic agents remove the inhibition of tumour-specific T cells and accentuate the body's immune response. There are currently 6 globally marketed PD-1/PD-L1 inhibitors. These are atezolizumab, avelumab, cemiplimab, durvalumab, nivolumab, and pembrolizumab.

NICE (National Institute for Health and Care Excellence) is a non-departmental public body, responsible for providing guidance to improve health and social care in England. Part of the NICE decision-making process involves economic analysis to ensure that the limited resources of the NHS in England are used for maximum gain. They measure the cost-effectiveness of a product. The efficacy is measured in quality-adjusted life years (QALYs), which allows for standardisation across drug types and treatment areas. Where the cost of a new treatment is higher, but it is more effective than the standard treatment available, an incremental cost-effectiveness ratio (ICER) is used, based on a monetary figure per QALY gained.

This review looked at the NICE recommendations for PD-1/PD-L1 inhibitors, the stated ICERs, and examined any differences between recommendations for use versus non-recommendations. The NICE database was used, search criteria and screening criteria applied, until a total of 19 records remained for quantitative analysis and 35 records remained for qualitative analysis.

The review found that there were significant differences ($p = 0.004$, $p = 0.024$, $p = 0.045$) across all three comparisons made. The three groups for comparison were; products recommended for routine NHS use, products recommended for use under certain conditions, and products not recommended for use. The mean values for the ICERs of groups 1-3 were £29,182, £41,261, and £60,222 per QALY gained respectively. It was concluded that a rough target ICER required for recommendation for routine use was below £30,000 per QALY gained, however additional considerations such as life-extending end of life treatment allowed for conditional recommendation with a larger ICER.

A rapid systematic literature review evaluating the optimal dose of eculizumab in patients with atypical haemolytic uremic syndrome

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Atypical haemolytic uremic syndrome (aHUS) is a disease of over activation and dysregulation of the alternative complement pathway (ACP). The complement inhibitor Eculizumab was approved by the FDA in 2011 and became the first line of treatment in aHUS patients. The recommended dosage and regimen was based mainly on clinical trials conducted in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH), therefore there is limited evidence to support the current treatment as being the optimal dose for aHUS

patients. Further analysis is required to identify the optimal dose and treatment interval time as well as the implications of lifelong treatment of eculizumab.

The objective of this thesis is to identify existing literature on eculizumab dosage and regimens in aHUS patients and provide an analysis of the available evidence supporting either the current dose recommendation or an alternative dosing schedule.

A rapid systematic literature review was conducted in Medline, Embase and SCOPUS using a predefined search criteria. All results were then screened to ensure they meet the eligibility requirements and underwent a data quality analysis check. Only publications that met the eligibility criteria and passed the quality analysis were included in the review.

The literature search identified 18 publications to be included in the review. The results included evidence to support a variety of different dose schedules, ranging from complete withdrawal to an increase in the dosing intervals. The results also highlighted alternative approaches to monitoring the effectiveness of eculizumab and the different factors such as genetic mutation which may also impact the optimal dose on a per patient basis.

The analysis highlighted there was no dominant evidence towards one specific optimal dose, but it did provide interesting approaches to disease monitoring which enable dose tapering to become a more practical option in the future.

JAK inhibitors as an intervention for the management of fatigue in rheumatoid arthritis: A systematic literature review and meta-analysis

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Fatigue is a common and distressing symptom for patients with Rheumatoid Arthritis (RA), there is no accepted evidence-based management guidelines. There is evidence to suggest that Janus Kinase (JAK) Inhibitors improve symptoms in RA as well as reducing joint damage and improving overall quality of life.

To evaluate the effect of JAK inhibitors on fatigue in rheumatoid arthritis.

The following electronic databases were searched up to 1 May 2021: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, Current Controlled Trials Register, The UKCRN Portfolio Database, and The National Research Register. In addition I checked the reference lists of articles identified for inclusion of additional studies.

Randomised controlled trials were included if they evaluated a JAK Inhibitor intervention in participants with rheumatoid arthritis and had self-reported fatigue as an outcome measure.

One reviewer selected relevant trials, assessed methodological quality and extracted data. Where appropriate this data was pooled in meta-analysis using a random-effects model, the results were presented using the Cochrane model of systematic literature review.

Switching from Adalimumab to Biosimilars: A rapid review of NHS England's approach to Shared Decision-Making

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Shared Decision Making (SDM) has gained attention exponentially in recent years and is now considered the gold standard model for making patient-centred healthcare decisions between patients and clinicians. The UK National Health Service (NHS) has long since been an advocate of Shared Decision-Making but the decision by the NHS Biologic Commission to switch at least 80% of all Adalimumab patients from originator to a biosimilar drug proved to be an unexpected challenge for effective patient involvement during implementation of the switch.

The objective of this research is to examine the strategies aimed at facilitating or improving clinician's adoption of shared decision making during the implementation of the biologic to biosimilar switch. The goal is to evaluate their effectiveness in order to make recommendations for a patient centred approach in implementation of future biologic switch programmes.

A systematic search of the literature was conducted from 4 scientific database libraries using a mixed approach of qualitative and quantitative methods. Screening and eligibility criteria was limited to peer reviewed publications from December 2018 to date and articles relating to the NHS or UK only. Both opinion pieces and evidence-based articles were included. A PRISMA approach was used for meta-analysis while thematic analysis was used to identify the strategies used in the hospitals to involve patients in shared decision-making during the biologic switch implementation. All the standard practices were observed in accordance with rapid review procedure.

15 full text publications were systematically selected and included in this review, each describing the Adalimumab switch in the context of SDM. 6 themed strategies were identified: informed consent was done27% of the time; only 33% carried out one to one consultations, 40% decision aids were used; patient education was carried out at 47%. At 93% ran dedicated biosimilar advice line, and at 100% all the articles reported sending out switch letters.

Results indicate that efforts were made to facilitate patient involvement to varying degrees. Literature suggests that there was no clear guidance given from NHS England on how to implement the switch to support SDM therefore it was not consistently executed within the NHS. While it was not unanticipated to find differences on how the switch was implemented between hospitals, the rate of difference was significant. These inconsistencies suggest a lack of unified understanding of what SDM involves. Based on these results, the conclusion can be drawn that patients were not adequately involved in shared decision making during the Adalimumab biologic switch programme.

Nottingham Palmar Plate Arthroplasty for Metacarpophalangeal Joint Non-Inflammatory Osteoarthritis

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The palmar (volar) plate interposition arthroplasty of the metacarpophalangeal joint is a well-established surgical technique for osteoarthritis. However, due to poor outcomes in patients with inflammatory arthropathy and difficulties with the surgical technique, its treatment has become less widely used (Trickett, R, W. and Oni, J, A. 2021). This paper reports on the outcomes of pain, function, and range of movement in patients treated with the novel Nottingham Palmar Plate Arthroplasty (NPPA) technique.

The aim of this study was to report the outcomes from patients who have received the novel NPPA for non-inflammatory osteoarthritis of the metacarpophalangeal joint.

A retrospective review of data for six patients that had received the Nottingham Palmar Plate Arthroplasty surgical technique for osteoarthritis was conducted. Review of routine data concerning pain, function and range of movement are reported.

The results of six arthroplasties in six patients are reported. Range of movement, finger pinch and hand power grip measurements improved generally post-operatively, however, no statistically significant differences were seen in any outcomes from baseline up until the final Week 52 timepoint due to the small sample size. The median pain score (Numerical Pain Rating Scale 0-10) reduced from 8 (baseline), to 1 (Week 52). No intra-operative complications or immediate post-operative complications were noted.

Despite the limitations to this study, the results show favourable improvements in pain relief and physical function for patients post-operatively. While the NPPA continues to be considered a treatment option for eligible patients, the recommendation for a larger cohort study with longer term follow-up should be considered.

Is there a role for Focal Adhesion Kinase (FAK) in Acquired Endocrine Resistance

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The acquisition of resistance to hormonal therapies in breast cancer is of increasing medical concern. Studies to date have highlighted a relationship between resistant cell lines and migratory phenotype. The intracellular protein focal adhesion kinase (FAK) modulates signalling pathways integral for migration and survival and is often aberrantly expressed in breast cancer. Owing to FAKs activity, this study aimed to identify whether the kinase plays a role in acquired endocrine resistance.

Western blot analysis was performed on endocrine-sensitive MCF-7 and endocrine-resistant TamR/FasR cell lines to evaluate expression levels of total-FAK, phosphorylated FAK and other implicated proteins. Immunofluorescence microscopy was performed to identify protein localisation and morphological differences between cell lines.

Densitometry analysis highlighted a significant upregulation of phosphorylated AKT in the tamoxifen-resistant TamR cell line ($P < 0.005$) and similar expression levels of FAK across cell lines. Immunofluorescence microscopy identified similar subcellular localisation of FAK and migratory phenotype in TamR/FasR cell lines.

These data would suggest that FAK may not play a pivotal role in acquired endocrine resistance, however, the upregulation of pAKT may indicate that FAK indirectly influences an oncogenic signalling pathway frequently deregulated in endocrine-resistant breast cancer.

Exploring a role for focal adhesion kinase (FAK) in TNBC vs. luminal A breast cancer

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The purpose of this study is to evaluate Focal Adhesion Kinase (FAK) expression levels and its prognostic significance across three major subtypes of breast cancer – Triple-Negative, Luminal A and HER2-enriched to assess the potential benefit of its targeting in anti-cancer therapy.

A rapid literature review was conducted using three independent electronic databases to identify good-quality publications that investigated the research question. Western blotting and immunofluorescence staining was performed to analyse FAK and associated interacting protein levels and their subcellular localisations across the cell lines MCF-7, MDA-MB-231 and SKBR3. Bioinformatics/proteomics resources were used to examine FAK both at the gene and protein level.

5 out of 6 studies established a significant association between FAK and TNBC ($p<0.05$). Western blot results demonstrated higher but nonsignificant differences in FAK expression levels in the MDA-MB-231 cell line (vs. other models, $p>0.05$). Immunofluorescence staining analysis revealed strong FAK cytoplasmic and peripheral staining in SKBR3 cells (85%). FAK mRNA expression was significantly correlated with negative ER ($p=2.97e-03$) and PR ($p=2.08e-03$) status. Survival analysis showed high FAK expression was associated with non-significantly longer OS, RFS and DMFS in basal tumours (vs. luminal) but nearly correlated to shorter OS in HER2+ tumours ($p=0.054$). Most frequently interacting proteins with FAK were found to be Paxillin, Src and p130Cas.

Our in vitro data demonstrate a strong potential for FAK as a promising therapeutic target, particularly in the triple-negative phenotype whilst further investigation is required to confirm the role of FAK in other breast cancer cell models.

Biosimilar implementation in the NHS, a rapid systematic review and analysis of prescribing trends and cost savings in Wales

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This review will be in two parts. The objective of the first section will be to examine the current literature to understand barriers associated with biosimilar uptake within the NHS. The second section will explore key issues from the rapid systematic review, these being whether large switch programmes are still taking place in Wales, and whether biosimilar to biosimilar switches are as cost effective as biologic originator to biosimilar switches.

Relevant literature was selected by carrying out a literature review in the Medline and Embase databases.

1000 articles (263 Medline, 737 Embase) were returned from the initial search criteria. Duplicated articles were removed along with ones which were not focused on the UK or did not have any UK authors. 103 remained and these were screened further with full text review with the research question in mind.

14 were then selected for quantitative analysis.

Prescribing data in Wales was examined, looking at both originator biologic and biosimilar prescribing rates, to look for trends and the cost savings generated.

The current rituximab biosimilar to biosimilar switch in Aneurin Bevan University Health Board (ABUHB) cost saving potential was calculated, to examine if biosimilar to biosimilar switches are as cost effective as biologic originator to biosimilar switches.

Literature included service evaluation, reviews and research studies. The research studies were mostly of a qualitative design. UK data was limited and only one study mentioned Wales specifically. Large switch programmes took place across the UK when the first biosimilars were approved, due to the cost saving driver. The majority of studies explored this, along with associated success and barriers. There is no evidence to suggest that biosimilars are inferior to originator biologics. Understanding nocebo responses are key, and special focus is given in the literature in preventing this.

Prescribing data in Wales is reflective of the move away from originator biologic to biosimilars. It is difficult to ascertain if the rate of switching has slowed with the current figures. Data is lacking in regards to biosimilar to biosimilar switches, and it is often questioned if these would be as cost effective as the initial biologic to biosimilar switches. Projected figures from the ongoing Rituximab biosimilar to biosimilar switch in Aneurin Bevan University Health Board, demonstrates that there is a large cost saving potential, with an anticipated annually saving of £114,000. Since biosimilar implementation, biosimilars are now even more readily available for patients, preventing disease activity earlier and ensuring a better quality of life and less demand on healthcare resource.

Biosimilar implementation has been utilised throughout the UK, and continues to be expand. It is now established that biologic to biosimilar switches are safe, and the treatments of equal quality. The education of patients on these medications are important, and needs to be done in a patient centric manner to prevent a nocebo response. Biosimilar to biosimilar switches are now beginning to happen, but there is limited guidance and data on how these should be approached and supported.

Does Targeted FLT3 inhibitors result in a better outcome for patients with Acute Myeloid Leukaemia with FLT3 (fms-like tyrosine kinase 3) mutated subset?

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A narrative systematic review to look at the benefits of introducing FLT 3 inhibitors into the treatment of patients diagnosed with acute myeloid leukaemia with FLT 3, and to see if targeted FLT3 inhibitors resulted in a better outcome for patients with Acute Myeloid Leukaemia with FLT3 (fms-like tyrosine kinase 3) mutated subset?

FMA tyrosine kinase 3 (FLT3) is the most common of all the mutations found in patients diagnosed acute myeloid leukaemia (Majothi 2020). Patients that have been diagnosed with FLT3 mutation tend to a poor prognosis and are more at risk on relapse (Kottarudis 2002). Through the course of this thesis, the author will be exploring the benefits of the introduction of FLT3 inhibitors into the treatment of AML FLT3 patients and how it effects their overall survival.

Investigating the Roles of Vestigial-Like Family Members in Breast and Reproductive Cancers

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Focal adhesion kinase (FAK) overexpression was reported to play a significant role in breast cancer development and progression, particularly in TNBC. This study explored if FAK expression (gene and protein level) is higher in TNBC than Luminal-A and its prognostic/therapeutic value in breast cancer. A rapid systematic review was conducted combined with bioinformatics/proteomics, laboratory work (Western blot and Immunofluorescence) and statistical analysis of data. Six studies were included in the review. The majority reported significant association of high FAK expression to high histologic grade, high Ki67, ER/PR- expression, EGFR+, p53+, TNBC and a poor prognosis/survival in breast cancer. The present study supported association to ER-negative (p=2.97e-03) and PR-negative expression (p=2.08e-03) but not to poor prognosis in TNBC. FAK expression was found to be significantly higher in MDA-MB-231 (Basal/TNBC) than MCF7 cells (Luminal-A) (p=0.0084). The expression of FAK interacting proteins SRC, MAPK, AKT, P130cas, paxillin, vinculin and E-cadherin were also found to play a significant role in breast cancer formation and metastasis. Overall, high FAK expression was found to be associated to TNBC and other poor prognostic factors but the association between FAK and prognosis varied between studies. Further studies are needed to examine its prognostic value and the potential of targeting FAK alone or in combination with its interacting proteins as a therapeutic approach in breast cancer, especially TNBC.

Do Statins Represent a Potential Treatment for Solid Tumours?

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Statins are among the most widely prescribed drugs worldwide as first-line medication for treating hypercholesterolemia. In addition to their lipid-lowering effects, statins exert anti-inflammatory, antioxidant and anti-proliferative pleotropic effects. Consequently, attention has been directed to the use of statins as an anti-cancer therapeutic, supported by preclinical studies. Thus, this systematic review aims to provide an understanding if there is sufficient evidence for the clinical application of statins in patients with solid tumours to improve mortality outcomes.

A search of PubMed, Scopus and Embase was performed to find relevant meta-analyses that investigated statin therapy in cancer patients published between January 2011 and July 2021, limited to the English language. Hazard ratio's (HR), 95% confidence intervals, heterogeneity and bias data were extracted directly from the papers to evaluate the effect of statins on all-cause mortality (ACM) and cancer-specific mortality (CSM). The quality of the meta-analyses was assessed using AMSTAR-2 checklist.

Sixteen meta-analyses of both observational and randomised controlled studies of 3,091,126 patients were included. Pre- and post-diagnostic statin therapy in colorectal, breast, prostate, lung, gynaecological, oesophageal and glioblastoma was investigated. Statin use showed compelling evidence to improve all-cause mortality (ACM) and cancer-specific mortality (CSM) in both colorectal and breast cancer patients, irrespective of timing of administration. While subgroup analysis indicated that KRAS-mutated colorectal and ER+ breast cancer patients have a survival advantage to their counterparts.

Our review supports the use of statins in the treatment of patients with solid tumours. Moreover, it identifies potential predictive biomarkers to identify patients that would benefit from statin therapy. Further research is warranted to clarify the role of statins, especially in the adjuvant setting, in the treatment of cancer through well-designed randomised controlled trials.

Exploring the Role of Pyk2 in Breast Cancer Subtypes

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Protein Tyrosine Kinase 2 Beta (Pyk2) is a protein that has been implicated in cell invasion and metastasis in breast cancer Pyk2 may also be involved in resistance to endocrine therapy in ER+ breast cancer. Therefore, it is possible that Pyk2 could be used as a prognostic/predictive biomarker or as a drug target in the future. However, the role of Pyk2 may differ across different breast cancer subtypes, which needs to be understood before Pyk2 can have any clinical value.

This study is a rapid systematic review combined with primary experimental data and analysis of publicly available datasets using open-access bioinformatic tools. Western blot and immunofluorescence microscopy were used to explore the expression and localisation of Pyk2 and related proteins in SKBR, MCF7 and MDA-MB-231 cells. Bioinformatic tools were used to analyse clinical data.

Inhibition of Pyk2 inhibits invasion-related processes such as TGF-β and ErbB signalling, invadopodia and focal adhesion development. Pyk2 expression patterns differ across different breast cancer subtypes. Studies reported that high Pyk2 expression is linked with metastasis and lower survival but results from bioinformatic investigation did not support this. Pyk2 expression is higher in cells resistant to endocrine therapy.

Pyk2 is involved in key EMT-mediating pathways. High Pyk2 expression may lead to increased metastatic potential and worsened prognosis in patients, but more research into the role of Pyk2 in different subtypes is needed before Pyk2 can be pursued as a prognostic biomarker or drug target. Pyk2 may have potential as a predictive biomarker for resistance to endocrine therapy.

Investigating the Role of Focal Adhesion Kinase as a Prognostic Marker or Therapeutic Target in Increasingly Aggressive Forms of Breast Cancer

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Breast cancer accounts for approximately 30% of cancer diagnoses in women, with TNBC being the most aggressive phenotype. FAK is a non-receptor tyrosine kinase responsible for activating many pathways promoting cancer hallmarks within TNBC. Using western blotting technique, it was determined there was significantly more MAPK protein present in TNBC ($p=0.0029$). Immunofluorescence showed total-FAK was highly increased in TNBC, E-cadherin was highly decreased in TNBC, total-FAK/vinculin co-localization was highly decreased in TNBC, and paxillin was highly decreased in TNBC. These findings support that there is increased FAK activation within TNBC. Utilising bioinformatic techniques, TNBC was found to have a higher log2 PTK2 gene expression when compared with both Luminal A ($p=0.0000021$) and HER2+ ($p=0.00067$). Additionally, there was a significant increase in the overall survival of patients whose PTK2 gene expression was low as compared with patients whose PTK2 gene expression was high ($p=0.047$). Rapid literature review techniques revealed several scientific papers which supported the idea of FAK being a possible therapeutic target through in vitro studies on cell models and clinical models, and in vivo studies on cell models within mice. In conclusion, FAK is a promising therapeutic target for TNBC.

The Role of FAK in Endocrine Resistant Breast Cancer

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Breast cancer cases represented the most commonly diagnosed cancer in 2020 and acquired endocrine resistance causes a clinical problem. Focal adhesion kinases (FAK) are involved with migration, invasion and survival in an array of carcinomas and these observations are present in endocrine resistant breast cancer.

A rapid review of 4 papers on FAKs in endocrine resistance alongside bioinformatic data were consulted. Laboratory studies on MCF7, TAMR and FASR cells were analysed for FAKY397, T-FAK and subsequent downstream pathway protein levels alongside cellular localisation to provide an overall conclusion on FAKs in endocrine resistance.

Rapid review analysis showed upregulation of FAKY397 in TAMR cells compared with MCF7 cells. Laboratory data showed T-FAK levels were significantly deceased in FASR cells ($p<0.01$) whereas the downstream pathway p-AKT was significantly increased in TAMR cells ($p<0.01$). Increased level of T-FAK, vinculin and paxillin at the plasma membrane of endocrine resistant cells was also observed.

Previous studies concur that FAKY397 and Y925 subsequently activate downstream pathways contributing to endocrine resistance. This report shows the importance of FAKs to an invasive phenotype in endocrine resistant cells, highlighting the main pathways activated throughout this process. Further studies must be performed to analyse these pathways inside a clinical setting.

The following abstracts have been withheld as they have been or will be published elsewhere, and/or due to intellectual property or confidentiality issues:

The Multifaceted Role of Vestigial-Like Family Members in Breast and Other Reproductive Cancers

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Investigating the Role of ZIP7 in Faslodex-Resistant Breast Cancer

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Could Vestigial-Like Family Members, VGLL1 Or VGLL3, Contribute to Resistance In Cancer?

Abbie Davies and J Gee

Investigating the role of Vestigial-like family members in breast and reproductive cancers

Brenna-Jasmine Forchin-Taylor and J Gee

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Investigating the Roles of Vestigial-Like Family Members in Breast and Reproductive Cancers

Lauren Hewitt and J Gee

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Investigating the role of Activated ZIP7 in Faslodex resistant compared to responsive breast cancer

Carwyn Hughes and KM Taylor

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Investigating the role of activated ZIP7 in triple-negative breast cancer

Benjamin Jarrett and KM Taylor

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Investigating the role of Activated ZIP7 in Faslodex resistant compared to responsive breast cancer

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Investigating the role of Activated ZIP7 in Faslodex resistant compared to responsive breast cancer

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Investigating the role of activated ZIP7 in tamoxifen resistant compared to responsive breast cancer

Matthew Norval and KM Taylor

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Do VGLL1 and VGLL3 contribute to an anti-cancer drug resistant phenotype?

Connor Parry and J Gee

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Are Vestigial-like Proteins 1 and 3 viable targets to combat cancer resistance?

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Investigating the role of activated ZIP7 in tamoxifen-resistant compared to responsive breast cancer.

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Investigating the Role of Activated ZIP7 in Tamoxifen Resistant Compared to Responsive Breast Cancer

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Investigating the Role of ZIP7 in Faslodex-Resistant Breast Cancer

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PhD Abstracts

Embeddable sustained-release microneedles for intradermal contraceptive delivery

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There is still an emerging need for effective, accessible and convenient contraception methods, particularly in low resource countries. Addressing this unmet need would reduce the incidence of unintended pregnancies and improve maternal and child health. Commercially-available long-acting reversible contraceptives (LARCs), such as subcutaneous implants (up to 5-7 years activity) and intramuscular injectables (3 months activity), maintain controlled daily release of hormones; thus, offer improved user compliance and convenience. They require however painful invasive administration and, in the case of implants, removal, typically by skilled healthcare professionals and generate biohazardous sharps waste. Microneedles are micron-scaled projections designed to puncture the uppermost layer of skin, stratum corneum, to facilitate transdermal or intradermal delivery of therapeutics into the cutaneous compartment, in a painless and blood-free manner. This thesis aims to develop an alternative method of contraception whereby the contraceptive is delivered into skin using microneedles which slowly degrade to provide 6-months contraceptive activity. Two biodegradable microneedle designs were manufactured by academic and industrial project partners. Candidate polymer formulations for the biodegradable microneedles were loaded with a synthetic progestin, levonorgestrel, and characterised for drug release kinetics. These studies were performed in conventional drug release media and a novel media supplemented with human skin homogenate. The use of these media, accompanied by sensitive and selective drug extraction and analytical protocols, enabled the characterisation of levonorgestrel release in a more biologically relevant environment. Sustained release kinetics of levonorgestrel were achieved from different biodegradable formulations in both media over a period of up to 9 months. The skin insertion performance of polymer only and levonorgestrel loaded biodegradable microneedles was assessed using human and porcine skin explants. In these studies, MN deployment was facilitated using several prototype applicator devices. Skin puncture experiments in ex vivo skin demonstrated that microneedles had sufficient tip sharpness and mechanical robustness to penetrate the skin surface. Microneedle performance varied between the polymer only and levonorgestrel loaded microneedles, with the microneedle composition and design, as well as the applicator mechanism, playing a key role in determining their efficiency. In conclusion, this thesis explored two novel designs of biodegradable polymer MNs to address the unmet need for contraception in low resource countries. The MN systems developed in this project hold great promise for sustained intradermal delivery of contraceptives for 6-months activity. This could provide an intermediate option to existing LARCs which have shorter, e.g. 3 months (intramuscular injections), or longer, e.g. 5-7 years (hormonal subcutaneous implants and intrauterine systems) duration of action. This MN-mediated contraceptive approach is also anticipated to improve user acceptability and compliance.

Biomaterial approaches for Glioblastoma therapeutics

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Glioblastoma (GBM) is one of the most aggressive malignant tumours of the brain and has a poor prognosis. The standard care of treatment of a patient diagnosed with GBM comprises total surgical resection of the tumour (if possible) followed by radiotherapy and an alkylating agent, temozolomide. However, despite the treatment, the tumour often reoccurs within or near the original region. Therefore, local delivery of therapeutics to GBM offers an advantage in targeting GBM recurrence or inoperable tumours. Other benefits of local delivery include minimising the systemic toxicity, bypassing the blood-brain barrier, and providing a tool to manipulate the microenvironments of the tumour, such as tumour hypoxia. Tumour hypoxia is associated with poor prognosis, increased aggressiveness, and treatment resistance. Chronic exposure to hypoxia triggers genetic adaptations orchestrated by hypoxia-inducible factor 1 (HIF1), which promote tumour survival and resistance. In addition, hypoxia interferes with the molecular effect of radiation, resulting in decreased radio-sensitivity by the tumour cells. In this thesis, we hypothesise that the use of nanotubes functionalised with carboxylic acid can be used to load and release doxorubicin efficiently intended for intratumoural injection for GBM. Moreover, an oxygen generation biomaterial can be used to reverse the hypoxia of GBM and enhance the radiation of GBM cells incubated in hypoxic conditions. Our first aim comprised developing delivery systems for GBM to deliver chemotherapeutics locally. Doxorubicin (a topoisomerase II inhibitor) was selected

for this aim because of its marked cytotoxic effect against malignant glioma cells in vitro (Wolff et al. 1999). We were able to prepare carboxylic acid-functionalised nanotubes (NTs) made of polyethylene glycol (PEG) that could load doxorubicin with an excellent loading efficiency and release it slowly. The doxorubicin loading into the NTs was achieved via electrostatic interactions between the positively charged doxorubicin and negatively charged NTs. The degree of drug loading by NTs could be tuned by varying the degree of carboxylic acid functionalisation. Doxorubicin loaded NTs decreased GBM cell viability in a dose-dependent manner. Our second aim involved the development of an oxygen-producing system to act as a radiosensitiser. Manganese dioxide (MnO2) nanoparticles were synthesised and surface modified with polyacrylic acid (PAA) to stabilise the nanoparticles in solutions. As a result, MnO2 nanoparticles were able to oxygenate 2D and 3D spheroid models and enhance the efficacy of ionising radiation. In addition, MnO2 were able to load and release doxorubicin over a long period, which could provide a multimodal system of oxygen-production and chemotherapeutic drug delivery. In conclusion, we have synthesised an injectable drug delivery system comprised of doxorubicin-loaded PEG nanotubes for the GBM. The system was successfully able to load and release doxorubicin. Moreover, we have synthesised an oxygen generating system made of MnO2, which was able to reverse the hypoxia and enhance the irradiation of the GBM.

Examining the role of ZIP7 in zinc signalling mechanisms and its relevance to cancer

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Zinc is an essential trace element in the human body. The cellular zinc level is tightly regulated by zinc transporters, including the ZIP family, which has a role in increasing cytosolic zinc levels. The aberrant function of many ZIP channels has been associated with human diseases, including cancer. Our main focus is zinc transporter ZIP7 which is uniquely placed on the endoplasmic reticulum membrane. The present study evaluated the significance of ZIP7 gene expression in breast cancer using comprehensive bioinformatic analysis. Additional experimental data generated within this project support the hypothesis that ZIP7 might be considered a predictive biomarker for breast cancer prognosis and a novel therapeutic target for breast cancer.

Understanding how age and biological sex influence the development of Alzheimer's disease

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Alzheimer's disease is a highly complex neurodegenerative disease and multifactorial. Age is the most significant risk factor for Alzheimer's disease (AD), with cases doubling every five years after 65. Thus, one of the most challenging areas in AD research is understanding what happens to the brain when it ages. Such insights could aid in distinguishing individuals who are more susceptible to developing AD during ageing. Over the last 25 years, brain ageing studies have looked at thousands of human brains to investigate the neuronal basis of age-related cognitive decline. However, most of these studies enrolled adults over 60 years of age. Therefore, those studies overlooked the most significant period of neuroendocrine changes in a woman's life, the menopause transition period. In the menopause phase, females undergo a significant decline in ovarian sex steroid production, including approximately 90% of oestrogen (E2) production. It is well documented that E2 has a neuroprotection function in the brain. Thus, the dramatic loss of sex steroids during menopause impacts multiple biological systems in the body, including the brain. In addition, despite documented sex disparities in the risk for dementia, the effect of biological sex and sex hormones on human brain ageing and AD development is understudied. Thus, in this thesis, it was hypothesized that an interrelationship between age and biological sex could impact brain structure and function during ageing and increase the susceptibility of women to develop AD. In this thesis, AD biomarkers and their processing proteins, along with E2-associated proteins expression, were investigated in frontal cortical brain samples from young (20-30), middle-aged (45-55), and elderly (70-90) males and females with no history of dementia, and in AD samples (70-90). A sex disparity during brain ageing and AD in the expression of AD biomarkers was reported in the first two experimental chapters, with females exhibiting age-related upregulation in the levels of APP and its amyloidogenic enzymes. Also, Aβ overproduction was observed in both sexes with advancing age, but its levels were significantly higher in aged female samples compared to aged males. In addition, higher levels of tau and GSK3β were found in

the aged female frontal cortex compared to the male frontal cortex. In AD samples, these sex disparities in AD biomarkers were also visible in higher Aβ levels and tau hyperphosphorylation in female AD patients compared to AD male patients. When E2-associated proteins were investigated, oestrogen receptor (ERα and ERβ), in male samples only ERβ and its downstream signalling molecules (Akt and ERK2) were upregulated in the male frontal cortex with ageing, reported in chapter 5, while middle-aged female samples have shown a decline in the level of ERβ and an age-related decrease in ERα in chapter 6. In AD samples, ERβ expression declined in males in chapter 5, and in females, both ERα and ERβ were decreased in chapter 6. Thus, the decline of ER in middle-aged females and AD of both sexes' samples could indicate a reduction in E2 neuroprotection function; E2 can regulate Aβ production, and it is the most significant neuroprotection function against AD. The neuroprotection of E2 against AD was illustrated in chapter 7, where the treatment of non-transfected female AD neuronal human induced pluripotent stem (hIPS) cells with E2 showed an apparent significant decline in Aβ levels. An inter-relationship between brain ageing and biological sex in AD development was apparent in this project. The findings of this project could partly explain the sex-based variation in AD development. ER decline in the female frontal cortex during ageing and tremendous overproduction of Aβ might highlight the differences between the sexes in the age of onset of AD. Preclinical AD could be initiated earlier in females because of losing the neuroprotective function of E2 during the menopause transition phase. Also, the thesis findings could indicate how important it is to investigate both sexes separately and not neglect to report female findings in preclinical and clinical studies where male samples were predominant.

Minimally invasive clinical monitoring and data transference in cardiac patients

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'Wet' electrodes used in electrocardiography (ECG), are applied to the surface of the skin to record cardiac activity. Over time, water-based electrolytic gels between the electrodes and skin dehydrate, reducing signal quality. Microneedle-electrodes negate the need for conductive gels and potentially improve signal fidelity by circumventing the stratum corneum and contacting the underlying conductive epidermal layers. This thesis aimed to assess the wearability and functionality of microneedle-electrodes in cardiac signal acquisition. Epoxy, 500µm-length microneedles were applied to excised skin models to assess insertion performance. Increasing downward application force increased microneedle penetration efficiency from 79%±8.20 (5N) to 87%±13.32 (15N). The microneedle application technique also had an impact on penetration efficiency, with impact insertion (93%±5.75) proving more effective than manual downward force (71%±22.01). Metallised versions of the epoxy microneedles were integrated into a commercial electrode and compared to conventional wet electrodes in human volunteers. Wet electrodes recorded higher quality signals than microneedle-electrodes in healthy human participants (1.6dB difference between the electrode types). This clinical data informed the development of an in vitro laboratory skin model to assess the influence of microneedle-electrode parameters on a simulated ECG signal. Increasing microneedle length from 500µm (25.2dB±3.25) to 600µm (24.3dB±2.31) did not result in a sustained improvement in signal quality ($p>0.05$). Bespoke second-generation microneedle-electrodes were manufactured allowing an improved signal quality to be maintained over the recording period (17.3dB±2.11 compared to 15.0dB±1.97 for wet electrodes; $p>0.05$) in the laboratory model. Human participant studies assessed their wearability and functionality. At rest, the metallised epoxy (23.2dB±5.79) and bespoke (22.5dB±7.57) microneedle-electrode performance was comparable to wet electrodes (24.9dB±6.44) ($p>0.05$). Under active conditions, the signal-to-noise ratio declined for all electrodes and ECG traces highlighted increased motion artifacts. Participants preferred wet electrodes and highlighted seven key wearability themes. Further optimisation of microneedle-electrodes for ECG monitoring is therefore, warranted.

An exploration of the prescribing and administration of medicines in a sample of UK care homes

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Residents of care homes are some of the most vulnerable members of society and are particularly susceptible to medicines harm. The safe and effective management of medicines helps to maintain or improve the quality of life of residents. However, there have been concerns surrounding poor prescribing and medicines

administration practices within the setting. The aim of this thesis was to explore current prescribing and medicines administration practices in a sample of UK care homes, and to understand whether senior carers could administer medicines safely and effectively. Medicines administration data was extracted from a digital medication management system (PCS™) to explore prescribing patterns, and medicines administration by staff in nursing homes. Semi-structured interviews and surveys were used to explore staff perceptions of senior carers administering medicines under the delegation of nurses. Analysis showed that a significant number of residents were prescribed medicines commonly associated with adverse outcomes in older adults. These included anticholinergic drugs (50%), hypnotics and/or anxiolytics (30%), analgesics (49%), and antimicrobials (24%). Although senior carers were at least as competent as nurses in administering medicines (no statistically significant differences in error rates; pvalue> 0.05), 92% of residents were exposed to medication administration errors during the three-month study period. Interviews and surveys explored staff perceptions of medication administration errors in care homes and a number of themes were identified notably the need for medicines training by senior carers. The findings from this thesis have highlighted that the quality of prescribing and medicines administration remains suboptimal in care homes, and the issues identified may ultimately cause resident harm. New models of care, such as senior carers administering medicines in nursing homes may fail if systemic issues which give rise to such issues are not addressed. Therefore, exploring strategies to efficiently safeguard the quality of medicines management in this setting should be prioritised.

Optimisation and enhancement of a liposomal delivery system

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Polymethyl methacrylate (PMMA) bone cement is commonly used for implant fixation in total joint replacement surgery (TJR), for the treatment of end stage arthritis. The use of antibiotic loaded bone cement (ALBC) is well-established in the prevention of post-surgical infections. Currently, elution of antibiotics from ALBCs occurs in a biphasic profile, with a high initial burst release within the first hours of application, followed by release of sub-inhibitory concentrations over long periods of time. Due to the inability of ALBCs to release clinically effective concentrations of antibiotic over an extended time-period, infections are still a major challenge; moreover, sub-inhibitory antibiotic release may increase the potential for antimicrobial resistance. The aim of this study was to develop and test a new bone cement formulation with optimised sustained antibiotic release, whilst maintaining the mechanical properties of the commercial bone cement. A liposomal bone cement delivery system containing gentamicin sulfate was produced and validated. The liposomal bone cement released a lower mass quantity of gentamicin than commercial ALBC; however, it released a higher percentage of its total incorporated gentamicin content compared to the commercial ALBC, whilst maintaining the antimicrobial efficacy and the mechanical properties of the commercial bone cement. Fluorescent labelled liposomes were used to determine that no measurable quantity of lipid was released from the bone cement. A freeze-dried liposomal formulation was investigated as a means to make the liposomal bone cement a more commercially feasible product. Gentamicin loaded liposomes were freeze-dried and incorporated into bone cement at gentamicin base concentrations of 0.15% w/w - 0.60% w/w of the PMMA bone cement. Whilst these cements showed improved antimicrobial properties, antibiotic release was generally below the limit of detection and mechanical properties were only maintained for the cement containing 0.15% w/w gentamicin. The process was also relatively inefficient, with freeze-drying causing a reduction in lipid and gentamicin content to around half of the initial mass quantities used. Given the limited functionality of the freeze-dried formulation and the commercial impracticality of the non-freeze-dried liposomal bone cement, alternative bone cement formulations were investigated. ALBC containing different mass quantities of hydrophilic (lactose) and hydrophobic (magnesium stearate) additives at concentrations of 10% w/w - 25% w/w of the PMMA bone cement were prepared. Cement containing lactose, released much higher mass quantities of gentamicin than the commercial ALBC and the magnesium stearate cements, although the magnesium stearate cements had a more gradual drug release profile. All cements containing additives had comparable antimicrobial properties to the commercial ALBC, however, the mechanical properties were only maintained for the 10% w/w lactose cement. Since magnesium stearate cements had a more extended drug-release profile, magnesium stearate was used to dry particle coat gentamicin sulfate using different mixing methods of varying shear (tumble mixer, pestle and mortar, ball mill). All bone cements made from dry powder coated gentamicin sulfate, released a similar mass of gentamicin, which was significantly lower than the gentamicin dose released in the commercial ALBC. Antimicrobial activity was maintained, and mechanical properties were comparable to the commercial ALBC. This research has shown that incorporating liposomal antibiotic formulations in bone cements, in a manner that is commercially feasible, is extremely challenging. Whilst the use of liposomes can improve the drug release profile, the manufacturing process can result in significant loss of the active ingredient. Dry

particle coating of gentamicin, using small mass quantities of magnesium stearate, could be used as an alternative approach to modify the drug release profile from bone cement, however, further investigation is required to optimise parameters such as mixing method, particle size and type of guest particle, and to establish the potential impact of this approach on toxicity and cement longevity.

Defining the role of epidermal lipoxygenases and its lipid products in skin homeostasis and disease

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Healthy skin forms an effective barrier that prevents infection and rapid water loss from the body. Epidermal barrier disruption is evident in common skin conditions such as psoriasis and eczema, along with significantly affecting adequate wound healing. Essential to a competent barrier are lipids which are metabolised by a group of enzymes known as lipoxygenases (LOX's). The molecular mechanisms by which LOX regulates skin homeostasis and prevent skin disease is unexplored and therefore defining the role of LOX in skin is the primary objective of this study. RNA-sequencing of 12R-LOX deficient and wildtype mouse models was performed and results analysed using various bioinformatics tools, allowing the identification of possible molecular networks and biological processes in which LOX may regulate skin function. Interestingly, Gene Ontology (GO) enrichment analysis identified enriched terms relating to differentiation including "keratinocyte differentiation", "keratinization", "peptide cross- linking" and "cornified envelope". Moreover, the majority of differentially expressed genes (DEGs) following 12R-LOX protein deficiency are localised to stratified epidermal layers, suggesting a possible role for 12R-LOX derived lipids in differentiated layers. Interestingly, upregulated genes with a 1.5 fold change included genes involved in the epidermal differentiation complex (EDC), such as small proline-rich protein 1b (Sprr1b), small proline- rich protein 2d (Sprr2d) and repetin (Rptn). KO vs. WT dataset also identified the statistically significantly downregulation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (Pparγc1α), hypothesised to be involved in regulating keratinocyte differentiation. As the RNA-sequencing data pointed towards a possible role for 12R-LOX in keratinocyte differentiation, investigation into the effect of 9R,10R,13R-TriHOME terminal product of the 12R-LOX / eLOX-3 pathway showed an increasing effect on the protein level of important differentiation markers (Ivl and Krt10), whilst further in vitro experiments ruled out a role in proliferation, migration and apoptosis respectively. It was also identified in this thesis that the 9R,10R,13R-TriHOME activates Pparγc1α, which was downregulated in 12R- LOX deficient vs wildtype and has previously been demonstrated to be implicated in the process of differentiation. Bioinformatics and biochemical data indicate a possible role for 12R-LOX derived lipids in keratinocyte differentiation which is an important process for the development of an effective skin barrier. These observations raise the possibility of utilising the 9R,10R,13R- TriHOME as treatment for skin disorders with a defective epidermal barrier function.

Targeting cancer stem cells via small molecule inhibition of c-FLIP

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The ability of cancer stem cells to self-renew indefinitely and differentiate into multiple tumour cell types has made their elimination critical to completely eradicate tumours. TRAIL (TNF-related apoptosis inducing ligand) is a death ligand that selectively induces apoptosis in cancer cells, but clinical trials utilising recombinant TRAIL or TRAIL agonists eventually failed due to the development of TRAIL resistance post treatment. c-FLIP inhibits TRAIL-mediated apoptosis and its overexpression has since been identified as one of the mechanisms of TRAIL resistance present in cancer stem cells. As a strategy to overcome TRAIL resistance, this project aims to develop new small molecule inhibitors of c-FLIP that re-sensitises cancer stem cells to TRAIL-mediated apoptosis. Twenty different compounds were identified through in silico screening as potential lead compounds targeting DED1 of c-FLIP. TKCC-05 pancreatic cancer cells and HeLa cervical cancer cells were treated with these compounds to test for their ability to sensitise cells to TRAIL-mediated apoptosis. The pan-caspase inhibitor Z-VAD-FMK was used to confirm apoptosis induced by the tested compounds was caspase-mediated. These compounds were also tested for their ability to inhibit the formation of MCF-7 colonies. Three out of

twenty compounds (A7, A12 and A13) in combination with TRAIL successfully induced apoptosis in HeLa cells rescuable by caspase inhibitor. A7 was the best candidate out of the three successful candidates, with an EC50 of 72.23 μM. Three out of twenty compounds (A5, A7, and A12) in combination with TRAIL reduced MCF-7 colony formation via sensitisation to TRAIL. A7 was the best performing candidate overall and was selected to be further optimised. Seventeen analogues of A7 were synthesised and tested, yielding the analogue KYL5 that showed an improved EC50 of 40.85 μM. Preliminary modifications to the drug candidate A7 had shown that lipophillic functional groups were favored for improved c-FLIP inhibitory activity. Further cycles of modifications and optimization will be done in the future to establish structure-activity relationships. Several amino acid residues in the DED1 pocket of c-FLIP were mutated to identify key residues important for c-FLIP's ability to bind onto procaspase-8 and FADD. HeLa cells expressing the 18-45 double mutant c-FLIP lost their resistance to TRAIL-mediated apoptosis, whilst cells expressing the R38A mutant c-FLIP did not respond to OH14 sensitisation. This had provided more information on the structure-function relationships of c-FLIP, and further evidence on DED1-mediated activity of c-FLIP. Overall, the project had successfully synthesised novel small molecules that showed c-FLIP inhibitory activity, and serves as an early proof of concept where pharmocological c-FLIP inhibition can be achieved. Whilst the analogue KYL5 is not ready for clinical testing, several opportunities for improvements are available for the candidate and will become the basis of future work.

Impact of complement regulator factor H on thrombin's role in fibrin clot formation and the anticoagulant protein C pathway

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Complement is part of innate immunity in blood plasma and contributes to eliminating pathogens and cellular debris from the host system. Coagulation is involved in haemostasis, enabling clotting after injury to a blood vessel. Both pathways are evolutionarily linked and composed of effector proteins called zymogens and regulators. Recently, increasing evidence has demonstrated the molecular interactions, or crosstalk, between complement and coagulation. Understanding the importance of the molecular crosstalk is key to further determine the impact of its dysregulation in diseases. A key step in the coagulation system is the generation of the enzyme thrombin which further enhances the pathway, and cleaves fibrinogen into fibrin to form a clot, preventing fluid loss. Thrombin is also tightly regulated to prevent excess thrombi formation, for instance through its interaction with endothelial membrane bound cofactor thrombomodulin, enabling protein C activation which downregulates upstream coagulation factors. Complement factor H, a key regulator of the alternative pathway in complement activation in the fluid phase and on cell surfaces, has been shown to interact with thrombomodulin, as well as other coagulation components such as factor XII, factor XIII, von Willebrand factor and platelets. However, the role and involvement of factor H in coagulation activation and regulation remains poorly understood. The aim of this work was to analyse the impact of factor H on thrombin's anticoagulant role in protein C activation, in the presence and absence of thrombomodulin, as well as on its procoagulant role, in the cleavage of fibrinogen into fibrin. Therefore, I developed biochemical assays to assess activated protein C generation, and thrombin-mediated fibrin clot generation in a pure protein system and in plasma, in the presence of factor H. Finally, I investigated the binding sites on factor H using SPR and binding assays supported by computational modelling. Factor H enhanced protein C activation by the thrombin/thrombomodulin complex but also by thrombin alone. It also enhanced the rate of fibrin clot formation and altered the structure of the clot. Absence of factor H in plasma increased clotting time and restoration of physiological levels decreased it significantly. Importantly, it was determined that thrombomodulin, and primarily thrombin, are ligands for factor H, and these interactions mediated these functional effects. It was also showed that the C-terminal domain of factor H is one binding site involved in the interaction with thrombin. To conclude, factor H could be a potential novel ligand for thrombomodulin and thrombin, regulating its pro and anticoagulant roles. This is relevant in iv diseases such as atypical hemolytic uremic syndrome (aHUS) where complement and coagulation are dysregulated due to mutations in factor

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Developing a 3D bio-printed human skin model

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Unravelling the pathophysiological mechanisms of skin disease relies on representative skin models. However, current laboratory skin models have acknowledged limitations which impede translation to the clinic. The need for a stratified 3D cellular co-culture with control over spatial organization to represent the complexities of human skin more realistically is therefore highly desirable. 3D bio printing has recently generated physiologically relevant human skin models (Baltazar et al. 2020). However, current bio printing technologies are typically expensive, difficult to operate, and have low customisation ability, thus hindering widespread accessibility (Ioannidis et al. 2020). Custom-built, low-cost 3D bio-printing platforms have been recently reported for the production of 3D cell culture and tissue models (Cubo et al. 2016a; Reid et al. 2016; Kahl et al. 2019; Ioannidis et al. 2020). It is therefore hypothesised that recreating the structure of human skin through developing a cost-effective flexible 3D bio-printing technology is feasible. The aim of this study is to develop a 3D-bio-printed human skin model using a low-cost flexible cell-printing platform. Preliminary 2D cell culture studies were conducted using an immortalized keratinocyte cell line to establish the optimum culture conditions. Cells were maintained in a proliferative or differentiated state by varying the calcium concentration to mimic the physiological epidermal calcium gradient (Wilson et al. 2007; Bikle et al. 2012). Morphology and specific biochemical markers of differentiation were studied in each condition. A bespoke LEGO® 3D bio-printer, capable of encapsulating high cell densities and creating 2D and 3D arrangements of cells, was built in parallel to the cell culture experiments. Cells maintained in low calcium exhibited proliferative characteristics whereas cells in higher concentrations of calcium were induced to become more differentiated, recapitulating the effect of the calcium gradient in the epidermis. The programmed custom-built LEGO® 3D bio-printer was optimized to generate high-resolution 2D and 3D complex patterns of bio-ink. Using the custom-built 3D bio-printer, the cells were successfully encapsulated in bio-material droplets and printed. Microscopy images and a cell viability assay indicated homogenous cell dispersion and high cell viability (87.5%) within the bio-printed material. Keratinocytes were successfully 3D bio-printed in an 18-layered squared lattice and imaged showing high cell viability. These initial results provide a platform for manufacture of single and mixed cell culture populations with a defined 3D organization, akin to the human skin. The adaptability and flexibility of the custom-built LEGO® 3D bio-printer has the potential to enhance the complexity of the skin tissue model. Therefore, a first prototype of the LEGO® 3D bio-printing platform has been developed demonstrating a printing resolution at the sub-millimeter scale, providing a cost-effective novel 3D bio-printing technology for the production of human skin models.

Design and synthesis of novel CYP51 inhibitors as therapeutics for candida albicans infections

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Lanosterol 14α-demethylase, CYP51, is an important target enzyme in fungal diseases. *Candida albicans* (*C. albicans*) is one of the fungal pathogens prevalent in human infections, which causes infections that range from superficial to life-threatening systemic infections, a particular challenge in immunocompromised patients. Although azoles (especially Fluconazole) have been used as a first choice for the treatment in many fungal infections and as a prophylactic, issues of drug resistance to this class of antifungals are increasing. The aim of this study was to design and synthesise novel CYP51 inhibitors that can counteract the azole resistance mechanism in *C. albicans*. Drug design employed computational methods: Molecular Operating Environment (MOE) for docking and binding studies and Desmond Maestro for Molecular Dynamic (MD) simulations to determine optimal fit in the CaCYP51 active site and binding interactions. From the computational docking study, thiazole, hydroxy-propyl benzamide and non-hydroxypropanamide novel compounds were selected for synthesis; a short series (fluconazole type), a mid-sized and an extended series (posaconazole type), which showed promising docking results. The extended series was observed to have optimal filling of the active site and additional binding interactions (H-bonding and π-π/hydrophobic) at the access channel that were anticipated to counteract the loss of one key H-bonding interaction with Tyr132, a common mutation in *C. albicans* azole resistant strains (Y132H, Y132F). Using 4-8 step synthetic schemes, all series were obtained

and compounds subject to structure (^{1}H and ^{13}C NMR, mass spectroscopy) and purity (HPLC) analysis. All final compounds for the thiazole (Chapter 2 and 3), chloro and dichloro of the hydroxy-propyl benzamide (Chapter 4) were evaluated against *C. albicans* strains (MIC) and promising compounds evaluated further for CaCYP51 binding affinity (K_d) and inhibitory activity (IC_{50}) in comparison with the standard fluconazole. Owing to the COVID-19 situation, the fluoro and difluoro compounds of the hydroxy-propyl benzamide series (Chapter 4) were screened first against the model organism *Saccharomyces cerevisiae* wildtype and single mutant strains using disk diffusion assay, and the most promising compounds were progressed for evaluation against *C. albicans* strains using disk diffusion assay and MIC in comparison with posaconazole. The hydroxy-propyl benzamide extended compounds (Chapter 4) (**57, 59**, **69** and **70**) were found to be active against *C. albicans* strains. The biological assessment of the non-hydroxy-propanamide compounds (Chapter 5) is still in progress. Those compounds with optimal activity will be further evaluated against CaCYP51 mutant strains as well as selectivity against human CYP51. Further testing against a wide range of fungal strain will be done for future work.

Unlicensed 'special' medicines; improving the patients' experience

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Unlicensed 'special' medicines are used frequently around the world. Often used to treat children, the elderly and those with complex or rare clinical conditions, unlicensed 'special' medicines have not been through clinical trials and are not manufactured in commercial quantities like licensed medicines. As a result of this, unlicensed 'special' medicines may be harder to access after discharge (Wong et al, 2006). The aim of the thesis was to explore the views and experiences of those involved in prescribing, obtaining, supplying and receiving unlicensed 'special' medicines in Wales, in the hopes of being able to provide evidence-based recommendations for change. A systematic review was conducted to identify factors within the literature that have been seen to impact the patient journey or patient care when receiving an unlicensed medicine in the UK. Semi-structured interviews were conducted with community pharmacy staff members (community pharmacists and community pharmacy technicians), prescribers (from within primary and secondary care), and patients (or the parents or carers of those) receiving unlicensed 'special' medicines. Analysis identified key areas where delays or disruption may occur and provides an insight into the views and experiences of those who prescribe, obtain, supply or receive unlicensed 'special' medicines in Wales. The findings highlight that there is a lack of consistency in the definitions provided for unlicensed medicines and the associated terminology, not only within the literature but also across guidance documents. The lack of consistency was reflected in the limited understanding of all participant groups around what unlicensed 'special' medicines are. The detachment between care settings within the NHS led to multiple areas where delays or disruptions were reported. Overall, the evidence suggests that healthcare professionals and patients would benefit from the creation of consistent guidance and a more integrated healthcare system.

The discovery and development of small molecule immunomodulators as potential therapeutics

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Cancer immunotherapy has become a new generation of cancer treatment as it implicated the involvement of key components from the immune system to fight cancer. While this field is thriving, a subset of T cells termed gamma delta T cells (γδ T cells) is now starting to receive attention in the development of immunotherapeutics. γδ T cells shares no similarity with the common αβ T cells in terms of antigen recognition. Indeed, antigen recognition by γδ T cells does not reliy on the MHC/HLA (major histocompatibility complex or human leukocyte antigen) system. These cells recognise non-peptidic small-phosphorus-containing-molecules (called phosphoantigens) leading to their activation. This thesis focuses on the phosphoantigen-derived activation of γδ T cells to discover and develop new molecules that could activate γδ T cells as potential cancer immunotherapeutics. To achieve this, a series of γδ T cell activators were designed and synthesised, and their drug-like properties were optimised. Encouragingly, these activators exhibited potent activation of γδ T cell

and effective lysis of cancer cells. Overall, this study provides important preclinical data on a new class of γδ T cell activators that have the potential to treat cancer.

The following abstracts have been withheld as they have been or will be published elsewhere, and/or due to intellectual property or confidentiality issues:

Developing phage display technologies for novel sheep antibody production

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Nurses and pharmacists as independent prescribers: what is effective clinical supervision?

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Pomegranate rind extract with Zn (II) combination as a new therapeutic agent for oral care products

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