Cardiff School of Pharmacy & Pharmaceutical Sciences Research Abstracts

24nd Edition
2024

Editors: R Thomas, D Routledge
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School of Pharmacy & Pharmaceutical Sciences
Cardiff University

Published by STS Publishing, Redwood Building, Cardiff CF10 3NB, Wales, United Kingdom

Published October 2024

ISBN: 978094897609

British Library Cataloguing-in-Publication Data.
A catalogue record for this book is available from the British Library.

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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 24th 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
October 2024

Sequence and structural comparison of MASP2 against coagulation and complement factors to quantify homology and facilitate the development of a selective MASP2 inhibitor as a therapeutic measure for coronavirus infections

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The complement system, a crucial part of innate immunity, involves three pathways: the classical (CP), the mannan-binding lectin (LP), and the alternative pathways. Complement serine proteases have homology with proteins of the coagulation system, resulting in crosstalk between the two systems.[1] Activated mannose-associated-serine protease 1 (MASP1) and 2 (MASP2) of the LP cleave factors in the coagulation cascade, affecting platelet activation and fibrin formation. MASP2 plays a key role in LP activation, and its interaction with the viral N protein has implications in infections with highly pathogenic coronaviruses, where its hyperactivation can cause severe lung damage, as a secondary result of these infections, making it a promising drug target for current and future-emerging coronaviruses.[2] Nafamostat, a broad-spectrum serine protease inhibitor, showed favourable binding towards MASP2, as well as other factors of the coagulation system.[2] This project focused on comparing MASP2 functional and structural characteristics with complement and coagulation factors, exploring its potential as an anti-inflammatory drug target relevant to coronavirus infections, whilst avoiding cross-reactivity with other serine proteases, by finding a selective candidate.

To quantify the homology between MASP2 and factors of the complement and coagulation system, their primary sequences were analysed and compared using BLAST in UniProt.[3] Crystal structures of the proteins were retrieved from the Protein Data Bank (PDB) and alignment and structural superposing were performed. Identity and similarity percentages of pairs of proteins were computed, by analysing specific functional domains, particularly the catalytic serine protease (SP) domain and the complement control protein (CCP) domains. The predicted binding of nafamostat to the active site of MASP2, coagulation factor XII (FXII), thrombin and plasmin was evaluated by molecular docking. A series of structural analogues of nafamostat, both commercial compounds and newly designed molecules, were also evaluated by molecular docking for their predicted binding to both MASP2 and FXII, to identify selective MASP2 inhibitors that could serve as therapeutic measures for coronavirus infections.

BLAST searches were performed to identify homology links between MASP2 and proteins of the whole human genome. A high percentage identity was found with C1s, C1r, FIX, FX, FXI and transmembrane proteases 2 and 6. Secondly, structural superposition between MASP2 and proteins with high sequence identity revealed high structural similarity in the active site between MASP2 and FXII, thrombin and plasmin, with the highest similarity found with FXII. Nafamostat was therefore analysed by molecular docking in the active site of all five proteins, to reveal potential binding differences that may be exploited to design selective inhibitors of MASP2. MASP2 and FXII were the proteins for which nafamostat showed the best docking scores, preferential binding, and best overall occupation of the active site. Next, a virtual database of commercial structural analogues of nafamostat was analysed by molecular docking in the active sites of MASP2 and FXII, confirming for most candidates a similar predicted binding to both proteins. A few molecules showed a more favourable binding towards MASP2 and were therefore selected for experimental inhibitory assays, although they are not predicted to have a high selectivity for MASP2 over FXII. Finally, a small set of four novel analogues was designed to maximise a predicted binding preference for MASP2 over FXII. Among these, a novel structural derivative of nafamostat is predicted to form more favourable interactions with MASP2 compared to FXII, with a lower docking score and a better overall fit of the active site. Importantly, this molecule is predicted to form a hydrogen bond interaction with MASP2 catalytic serine, Ser633.

The homology data, from the computational comparison, will provide helpful insights on structural similarities of complement and coagulation serine proteases for researchers developing new therapies targeting these factors. The molecular docking experiments carried out on nafamostat and its analogues have enabled the design of novel compounds with key modifications, which are predicted to have increased selectivity towards MASP2. These molecules will now be synthesised and tested for their ability to selectively inhibit MASP2, possibly enabling the development of a new therapeutic option for infections with present and future-emerging highly pathogenic coronaviruses.

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An investigation into the potential link between menopause and suicide- a rapid review

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Menopause, a natural transition that affects all women, is defined by the absence of menstruation for 12 consecutive months. It is a result of a decline in ovarian function with a variable age of onset ranging between 40 and 54[1]. Multiple factors play a role in determining the age of onset and the transition is accompanied by a wide range of endocrinological, physical and psychological changes. A significant body of research is focusing on cognitive and mental health decline during menopause[2]. However, the possible association between menopause and suicide has been understudied[3]. This rapid review aims to explore the available literature to investigate the link between menopause and suicide.

Adhering to PRISMA guidelines, a comprehensive search was undertaken across the 3 databases: Scopus, Medline, and Ovid. Medical Subject headings (MeSH) terms were employed to ensure all appropriate studies have been captured. After applying the inclusion and exclusion criteria, 10 papers were eligible for the review.

One of these studies was identified by the 'snowballing' method applied to the already screened literature. Quality of the studies were assessed by using the Critical Appraisal Skills Programme (CASP). The data extraction process was systematically conducted from all the studies chosen. This involved identification and collection of key factors, results, and relevant points from each study, this was applied consistently to ensure reliability of the findings.

All the chosen studies observed a clear link between different stages of menopause and self-reported mental illness including anxiety, depression, and suicide ideation. Two studies investigated blood samples to ascertain the hormonal status and its link with symptoms with low Estradiol state correlating with suicidal behaviour. Three studies including large cohort sizes found a noteworthy association between menopausal transition and suicide ideation and attempts. Contrary to this, two studies discovered that depressive symptoms and suicidal ideation were most prevalent in postmenopausal women. Early menopause, whether this was surgically induced or natural, demonstrated more severe levels of depression.

While current research indicates a link between menopausal transition and suicide, there is a lack of robust evidence between clinical menopausal status and suicide ideation. The available research also fails to address pre-existing mental health issues, family history of mental health and a clear hormonal status at the time of suicide ideation. Large scale longitudinal studies including women with and without pre-existing mental health disturbances need to be carried out at different stages of menopause with correlating hormonal and biochemical parameters before a firm causal link can be established.

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The use of patient-specific human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) as a cell model for arrhythmia

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare genetic cardiac disease characterised by abnormal heart rhythms triggered by adrenergic stimulation, caused by genetic mutations in the gene encoding the cardiac ryanodine receptor Ca^{2+} release channel (RyR2). The resulting ion channel dysfunction

causes spontaneous Ca^{2+} leak from the sarcoplasmic reticulum (SR), leading to fatal arrhythmia. (1) Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) offer a promising model for studying CPVT, allowing for investigating disease mechanisms and the development of personalised treatments.

This rapid review assesses the current state of research on using hiPSC-CMs to model CPVT phenotypes. By summarising existing studies, this study highlights whether hiPSC-CMs constitute an accurate and useful model of CPVT pathophysiology and advancing drug discovery efforts.

The databases used to collate papers were Scopus, Medline and Google Scholar, using search terms 'human induced-pluripotent-stem-cell-cardiomyocytes' OR 'hiPSC-CMs' AND 'catecholaminergic polymorphic ventricular tachycardia' OR 'CPVT' AND 'calcium signalling' AND 'RyR2 receptor' AND 'Heterozygous mutation'. Studies referenced within the papers collected were also included if they answered the research question. Using a modified CASP framework (3) the studies were critically assessed. Studies which exhibited Ca^{2+} measurement experiments on CPVT variants were brought forward for further assessment. Mutation variant, cell origin, experimental conditions, measurement methodology and therapeutic implications were extracted for further analysis.

Sixteen studies were collected which met the inclusion and exclusion criteria. Of these, ten specifically investigated Ca^{2+} release (either global transients or in the form of Ca^{2+} sparks) in hiPCS-CMs heterozygous for RyR2 mutation from patient-derived dermal or blood cell sources. Of these, six studies monitored action potential morphology in addition, eight looked at the effects if adrenergic stimulation by isoproterenol or forskolin studies and five studies looked at drug effects on lowering the high adrenergic responses (most studies looked at more than one technique). The general trend across all studies was a significant increase ($P<0.05$-0.0001) in Ca^{2+} spark frequency in hiPSC-CMs compared to the control cell lines. Ca^{2+} transient amplitudes differed across studies, and this was hypothesised to be due to cell SR Ca^{2+} content at baseline. Upon adrenergic stimulation, CPVT hiPSC-CMs displayed increased Ca^{2+} abnormalities, sparks and action potential defects compared to control cells. Data on the effects of therapeutics: carvedilol; nebivolol; flecainide; propranolol; and nadolol, were varied but ultimately showed reduced incidences of Ca^{2+} abnormalities and delayed afterdepolarisations. One paper explored the effects of inhibition of calmodulin-dependent kinase, which strongly reduced Ca^{2+} spark incidences and afterdepolarisations, suggesting potential future therapies beyond β-blockade. (2) Overall the hiPSC-CMs models recapitulated the patient phenotype in response to drug therapy.

The findings across the studies provide direct evidence for important characteristics of CPVT CMs, for example where there are significant Ca^{2+} handling abnormalities it is indicative of the proarrhythmic nature of CPVT. However, the types of Ca^{2+} release events measured (Ca^{2+} sparks, transients, frequency and amplitude) were different across the studies, which made it difficult to draw parallels. In these current studies, the authors assume the cell models represent CPVT because of the observed Ca^{2+} dysregulation. However, there is a need for deeper research on whether cell genomes or mutation variants are causing variance in CPVT phenotypes and symptomology. Although patient drug sensitivity is recapitulated in vitro, there has been no attempt to explore the cause as to why there is variance in patient sensitivity to the different drugs. To know what fundamentally causes the differences in Ca^{2+} behaviour which leads to varied findings there needs to be strong and consistent data between the cell origin and its phenotypes. Morphology is a key driver for this field of research in the hope of valid representation of the CPVT CMs, however, the current studies have not succeeded in developing mature CMs which function realistically to give comprehensive evidence on the use of hiPSC-CMs for in vitro CPVT modelling, mechanism of CM dysfunction and patient-specific medicine.

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Examining the Long-Term Stability and Efficacy of Dinoprostone, Midazolam, Morphine and Rocuronium in Intravenous Infusion Preparations in Children and Neonates

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Intravenous infusions are a common route for drug delivery in neonatal populations. Infusion solutions currently are made up aseptically per patient, using a weight-based approach. With such small concentrations and volumes of drug required, there is room for error in calculating correct dosages and contamination of infusion solutions[1]. Mass production of standard solutions would greatly reduce this; the NHS has thus produced a framework for this[2], but stability of the infusion solutions must be ensured. This research aims to evaluate the existing evidence on long-term stability of parenteral preparations for four drugs commonly used in neonatal intensive therapy units: dinoprostone, midazolam, morphine and rocuronium and their suitability for mass production whilst maintaining safety and efficacy for neonatal populations.

A rapid review approach was adopted. Databases Embase + Embase Classic (Ovid), Scopus and Google Scholar were searched using keywords (dinoprostone OR midazolam OR morphine OR rocuronium) AND (stability OR shelf-life OR storage) AND (parenteral OR intravenous OR injection). It was decided that at subcategory specifying children and/or neonates narrowed the search, removing many relevant papers. Studies were critically assessed using a modified CASP framework for a laboratory experimental-based research papers. Studies that demonstrated experimental measurement of drug stability were taken forward for further review. Stability data, sterility, high-performance liquid chromatography (HPLC) results, and stability conditions were further analysed.

Twelve publications met inclusion/exclusion criteria and were taken forward for analysis. Of these, four publications discussed the stability of morphine, five studies for midazolam, two studies for dinoprostone and only one publication discussed the stability of rocuronium. All twelve papers used HPLC analysis, as well as other methods to test the stability of parenteral solutions. Data on drug stability was inconsistent across studies, with ranges from three years to 48 hours, with storage conditions from refrigeration to room temperature. However, many papers, despite producing adequate information on chemical stability based on the NHS gold standard[3], did not take into account microbiological factors and sterility in the infusion solutions.

There is limited evidence to suggest that we are at as stage to enable the mass production of neonatal infusion solutions of morphine, midazolam, dinoprostone and rocuronium based on stability data alone. There is more evidence suggesting that morphine and midazolam solutions may be suitable for mass production; including a promising morphine sulfate study that that uses terminal sterility via autoclave to ensure longevity along with safety and efficacy[4]. There is not yet sufficient evidence for the long-term stability and sterility of dinoprostone and rocuronium solutions. More studies are needed to assess the possibility of terminal sterility, as well as the chemical stability of these infusion solutions to allow for mass production, thus reducing the risk of errors in dosing of neonatal populations.

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Rapid review of methods of protection for the delivery of biologically active therapeutic agents orally into the intestine, for the treatment of Clostridium difficile infection

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The oral delivery of biologics is challenging due to the hostile environment confronted in the gastrointestinal tract (Gi). Challenges include the acidic conditions encountered in the stomach and subsequent enzymatic

degradation in the intestine.[1] These challenges need to be considered when attempting to develop orally delivered biological alternatives to the standard antibiotic treatment for Clostridium difficile infections (CDI).[2] The standard antibiotic treatment poses challenges due to various reasons, including microbiome disruption, the risk of recurrent infections and the potential for antibiotic resistance to develop, highlighting the need for alternative and more targeted therapies.[3] This rapid review aims to identify a manageable number of relevant papers, determine the evidence of protection and rationales, assess treatment effectiveness, and propose the most viable option for further development.

A rapid review methodology was conducted. Search terms were derived from the review title, and the key terms were searched in the following databases: SCOPUS, Ovid Medline and Embase (between January 2015 to December 2020). Search terms included: 'Clostridium' OR 'Clostridioides' AND 'Oral' AND 'Protein'. The search included in-vivo animal, human and in-vitro laboratory studies. The resulting papers were screened against predefined inclusion and exclusion criteria and eligible papers were assessed for bias using CASP checklists. PRISMA flow diagram was utilized to record the number of papers initially identified, followed by the screening process that led to the selection of final papers, which constituted the focus of the analysis.[4]

A total of 12 papers were identified, including in-vivo animal, human and in-vitro studies. The biological agents alternative to CDI antibiotics were 7: Phage, enzymes, antibodies, bacteria, yeast, Faecal microbiota transplant (FMT) and FliC proteins. Five distinct methods of protection were identified: encapsulation, bacteria and yeast as delivery vehicles, phage as a delivery vehicle, and anti-CD-WPI delivered in a buffer. Encapsulation techniques included: encapsulation within triple layers of gelatine, encapsulation within Enteric-coated AR Caps®, encapsulation within Chitosan-Ca pectinate microbeads, encapsulation within alginate hydrogel microbeads, and encapsulation within enteric-coated pellets, employing an outer layer of EUDRAGIT® L 30 D-55 polymer-based formulation.

Although deriving robust conclusions from the 12 studies proves challenging due to their diverse methodologies and models, the utilization of encapsulation proves to be the most reliable approach to protecting the therapeutic agents. Oral FMT emerges as the most effective strategy for addressing CDI. This method stands out for its maturity and refinement compared to the others, with clinical trials demonstrating highly encouraging outcomes. These trials signify the method's effectiveness and suggest a promising future trajectory. Nevertheless, additional efforts are required to actively pursue a specific avenue based on the insights gained from this review.

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Rapid review of B cell epitopes within the Protective Antigen of Bacillus anthracis which bind protective, toxin neutralising antibodies

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The threat posed by anthrax, a disease, caused by the Gram-positive bacterium Bacillus Anthracis, has been amplified by concerns over the potential use of anthrax spores as bioweapon[1,2]. This has spurred interest in the development of vaccines capable of protecting all members of the human race as studies have shown that the quality of the vaccine induced immune response is influenced by the genotype of the immunised individual[3]. Protective antigen (PA), the key protective immunogen in human and animal vaccines, is a component of the bacterium's tripartite toxin and is responsible for transporting enzymically active components of the toxin across the cellular membrane. This process can be blocked (neutralised) by antibodies which bind to epitopes located within the four domains which make up PA[4]. This project aims to identify the key immunodominant epitopes located within individual PA domains through a comprehensive analysis of the literature, with the ultimate goal of aiding the development of more effective vaccines.

The following databases, Medline (Ovid), Google Scholars, Scopus, and Cochrane Library were screened for relevant publications using specific search terms. Papers identified by this process were then screened for

relevance and selected studies were critically appraised using the CASP checklist tool. Key information was extracted from each study and key epitopes were identified.

Ten studies were included in the analysis of which seven identified epitopes within animal studies, one focused on human studies, and two examined the impact of HLA diversity on the human immune responses to anthrax vaccination. Domain four of PA, the region which binds to host cell surface receptors, contained the most epitopes many of which demonstrated neutralising activity using animal serum. Domain 2 also bounds animal derived neutralising antibodies while domains 1 and 3 contained the fewest neutralising epitopes. The neutralising epitopes identified in the human study recognised similar epitopes to those reported in the animal studies within domains 2 and 4. Lastly individuals belonging to the DR and DQ haplotypes generate significantly lower PA specific antibody responses than other HLA types when immunised with a PA based vaccine suggesting that an individual's genetic background may impact on the spectrum of epitopes which are recognised.

In conclusion neutralising epitopes within domain 4 affecting the binding of PA to cellular receptors, which are shared across species represent potential targets for future vaccine development. Variations in human genetics have been shown to significantly affect the quality of the PA specific immune response, with certain HLA types, predominantly found in Caucasian individuals, demonstrating a weaker response. This underscores the critical role of immune system processing of epitopes and the need for more inclusive studies encompassing diverse demographics. To fully realise the potential of these animal-derived neutralising epitopes for more effective human anthrax vaccines, further studies across different HLA type are imperative.

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Biocompatibility Assessment of 3D Printed Polylactic Acid Inserts for a Perfusable Cassette System: A Novel Approach to Vascularisation of Epidermal Models

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Medical utilisation of 3D printing is expanding. Many medical devices and implants are created using this technology[1] and research has shifted towards biomimetic tissue and organ fabrication[2]. The benefits involved with creating organs that mimic their physiological equivalents are vast and have the potential to revolutionize drug discovery and disease modelling, among others[3]. However, many challenges remain, and vascularisation perhaps being one of the most important. Vascular networks are essential for cell survival, oxygen and nutrient delivery to keep cells functioning, and are vital for complex engineered organs to possess prior to commercialization[4]. We propose a perfusion cassette, 3D printed using polylactic acid (PLA), could overcome this issue and enable fabrication of an in vitro vascularised epidermal model. To establish whether this plastic is an appropriate material of choice, this research sets out to determine the biocompatibility of 3D printed PLA inserts in comparison to standard cell culture plates.

Intricate designing using a computer-aided design software – OpenScad – was adopted to create the PLA insert. The insert was designed to slot into a standard cell culture plate where cells could be added to the surface. After each modification to the design, the PLA inserts were 3D printed using Ultimaker 2+ printer until the desired structure was achieved. The epidermal cells used were fibroblasts, these were 3D printed and cultured prior to any laboratory testing. Two standard six cell culture plates were set up. Each contained three control wells without insert and three with the PLA insert and a volume of media containing 500k cells was added to every well. The plates were incubated for 24 and 48hrs respectively. All experiments were conducted under aseptic conditions using 70% ethanol as a disinfectant. Prior to the cell counts, the fibroblasts were observed and imaged under a light microscope after 24hrs, and the process was repeated at 48hrs with the 2nd plate. Cell counts were taken following the respected incubation times and any similarities or differences between the control and the PLA inserts were used as a determinant of biocompatibility.

Observations indicated an increase in fibroblast numbers, with more densely packed cells in the 48hr plates compared to the 24hrs. The fibroblast numbers increased by an average of three-fold in the 24hr plates, and displayed consistency between the control and the PLA inserts. However, the 48hr counts showed some inconsistencies which can be explained by a leaking insert and issues with cell collection from the inserts. The fibroblasts showed no sign of cell deterioration or death, and the polymer exhibited no toxicity or inhibition to cell mitosis.

The findings in this study support the use of PLA in the creation of a perfusion cassette based on its confirmed biocompatibility. The anomalies in the cell counts do not impact the biocompatibility results as they are not due to reduced cell numbers, rather the characteristics of the polymer. Therefore, it would be wise to test the stability of the polymer ensuring it is durable and can perform its function for a suitable amount of time without disintegration or damage. A vascularised epidermal model has the potential to be used in many clinical applications like, wound healing studies, disease modelling, drug testing, among many more. Although this remains a distant goal, this research represents significant advancement in achieving it in the foreseeable future.

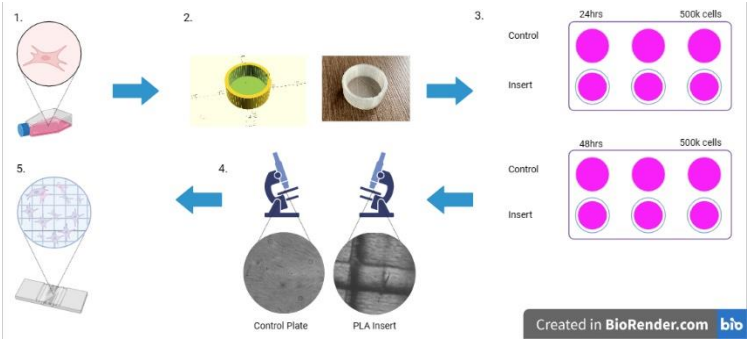

Figure A1: Graphic summary of the key stages in the methodology. (1) Represents fibroblast printing and culture followed by the designing of the PLA insert using OpenScad with the final 3D print (2). (3) Set up of the experiment, two culture plates each containing three control plates and three with PLA inserts filled with media containing 500k cells. (4) Images and observations of cells after respected incubation times with cell counts taken using a haemocytometer (5).

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A Study into the Biocompatibility of Fibroblast Cells with 3D-Printed PLA for Developing a Perfusion Cassette Enabling In Vivo Vascularisation in a Skin Model

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2D cell cultures have served to enhance scientific research, playing a major role in the study of cell division, apoptosis, and improving the understanding of various disease mechanisms[1]. A drawback of 2D cell cultures is that they are not representative of an in vivo environment[1]. Due to being grown in a static and rigid monolayer, 2D cell cultures lack the complexity and 3D structure found in vivo, thus limiting their physiological relevance[2]. Conversely, 3D cell cultures capture 3D tissue complexity and structural organisations making them a superior model for scientific research[3]. A limitation to static 3D cell cultures is the absence of circulating fluid preventing continuous nutrient supply to proliferating cells and the removal of waste by-products. To overcome this limitation a perfusion cassette is designed. It provides a continuous flow of nutrients for cells while removing waste by-products, establishing a microcirculation which better stimulates in vivo environments[4]. During this study, the aim is to investigate the biocompatibility of PLA with human fibroblasts. Favourable biocompatibility will allow PLA to be used in the development of a perfusion cassette, allowing for the in vivo vascularisation of a skin model, with potential benefits such as contributing to understanding skin biology, helping improve medical treatment and reducing the need for animal testing.

A PLA insert was designed using the software SCAD and fabricated via 3D printing using an Ultimaker printer. The insert was placed within a 6-well plate and 500,000 fibroblasts were seeded. Their viability was assessed after 24 and 48 hours. An empty 6-well plate with no inserts was used as control.

Results indicated that the fibroblasts were still viable and proliferative up to the 48-hour mark; the number of fibroblasts present more than doubled after 24 hours reaching 1,383,000 in the wells containing the PLA, and 1,975,000 in the control wells. From 24 to 48 hours, the number of cells in the control well increased from ~1,975,000 at 24 hours to ~2,150,000 after 48 hours. The increase seen in the wells containing the printed PLA insert is not as large with an increase of 36,000 cells, from 1,380,000 at 24 hours to 1,416,000 at 48 hours. A factor contributing to the reduced cell count is the migration of the fibroblasts into the pores on the PLA inserts. Although this made the cells challenging to visualize giving rise to an underestimate in the cell count, it suggests biocompatibility. If time permits further investigations into optimal pore size and porosity would provide further insight. Another possible reason for the lower cell counts may be the lightweight nature of the insert. During the experiment, it became evident that the insert lacked sufficient weight to remain stable within the wells when the media was added, causing air bubbles to form. Cell damage or death may have occurred due to hydrodynamic stresses caused by air bubbles bursting at the air-liquid interface, giving rise to the lower cell count. This highlights the importance of minimising the formation of air bubbles when designing the perfusion cassette.

Despite these limiting parameters, the study determines that PLA is a suitable material for constructing a perfusion cassette. When designing the perfusion cassette consideration should be given to optimal pore size, implementing strategies, such as debubblers, to minimize air bubble formation and ensuring an effective way to supply nutrients and remove waste by-products. The perfusion cassette will create an environment which favours the growth of a vascular network within a skin model. This will contribute to wider scientific research by bridging the gap between in vitro and in vivo studies. The vascularised skin model will have various uses such as being used in the treatment of burns and scars as well as providing a platform for topical and systemic drug discovery.

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Small molecule inhibitors of *Candida auris* – progress and challenges

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Candida auris (*C. auris*) is a highly virulent pathogen that potentially leads to invasive infection with nosocomial outbreaks in multiple countries including the UK. *C. auris* is a challenging-to-treat fungal pathogen due to drug resistance to most available antifungal agents. The CDC reported that 90, 33, and 5 percent of *C. auris* clinical isolates are resistant to fluconazole, amphotericin B, and echinocandins, respectively[1,2]. To address this *C. auris* drug resistance, alternative antifungal agents are urgently needed.

In this systematic review, relevant literature was searched in Embase, Scopus, and Web of Science databases. The search terms and keywords were derived from the research question using the PICO tool. Peer-reviewed, original research papers were considered without any time limit up to 21 November 2023. Articles were then screened for relevancy using the title, abstract, and full text of the articles available through the Cardiff library service. Only articles written in English were included in the study. From selected articles, the antifungal susceptibility and/or *in vivo* treatment outcomes of *C. auris* infections were extracted and compared using the minimum inhibitory concentrations (MICs) or related parameters.

During database and hand searching, 267 articles were found, of which 13 were eligible for inclusion in the current study. *C. auris* infection animal models have been studied in 2 articles, clinical data in 4 articles, and *in vitro* antifungal susceptibility in 7 articles. *C. auris* resistance data of selected antifungal agents studied in all 13 articles are shown in Figure 1. All the *in vivo* studies fulfilled the CASP criteria except 3 articles that had less precise results. All *in vitro* studies have fulfilled the adapted CASP checklist for assessing except 2 articles where the statistical analyses were not reported.

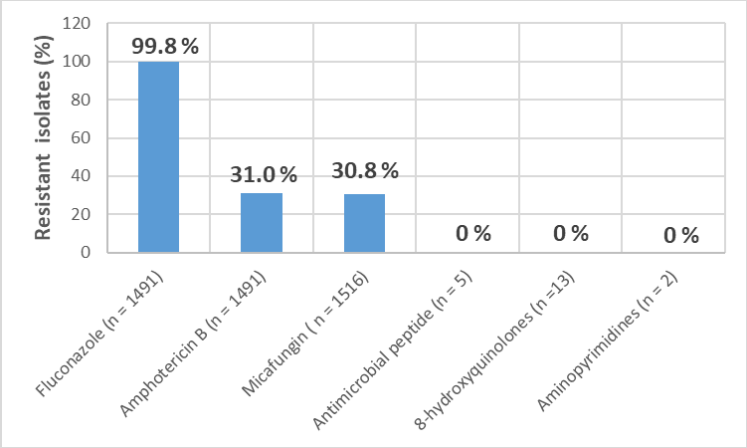

Figure 1: *C. auris* antifungal resistance data of selected drugs representing standard-of-care (fluconazole and amphotericin B, micafungin) and novel agents (antimicrobial peptides, 8-hydroxyquinolones, and aminopyrimidines).

Antifungal susceptibility results showed that *C. auris* is resistant to most standard-of-care antifungal agents such as fluconazole and amphotericin B (MIC > 250 µg/mL), while Echinocandins such as caspofungin and micafungin showed higher sensitivity (MIC < 3 µg/mL). On the other hand, repurposed 8-hydroxyquinolines, synthetic peptides, and aminopyrimidines fungicidal compounds showed promising inhibitory effects against *C. auris* (MIC, 1-25 µg/mL) with novel mechanisms of action. This could pave the way for developing better antifungals by overcoming the current resistance mechanisms of *C. auris.*

Limitations for the studies included: all clinical studies were retrospective in nature with no randomised trial; inaccuracy of measured treatment outcome in one skin infection model because of variation in the extent of infection between individual animals; 2 studies had low sample sizes (n = 2-5).

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RyR2 Phosphorylation and Neuronal Hyperactivity: Implications for Calcium Dysregulation in Alzheimer's Disease Pathogenesis. A Rapid Review

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Alzheimer's disease (AD), the foremost cause of dementia worldwide, is pathologically hallmarked by the accumulation of amyloid-β (Aβ) plaques and tau neurofibrillary tangles, which are central to the widely accepted Amyloid Cascade Hypothesis. This theory posits that the accumulation of Aβ initiates a pathological signalling cascade, resulting in tau pathology, neuronal loss, and synaptic dysfunction, culminating in the cognitive deficits characteristic of AD[1,2]. However, emerging research has spotlighted calcium (Ca^{2+}) dysregulation leading to neuronal hyperactivity as a pivotal, yet under-appreciated, facet of AD's pathophysiology[3]. At the core of this dysregulation are ryanodine receptors (RyRs), which play a crucial role in modulating intracellular calcium ([Ca2+]i) levels [4]. Alterations in RyR function and expression have been shown to exacerbate Ca^{2+} imbalance, fuelling aberrant neuronal excitability and furthering disease progression[4]. This rapid review explores the role of the RyR2 isoform in AD pathophysiology, focusing on two interrelated themes: the induction of neuronal hyperactivity by RyR2 dysfunction and the role RyR phosphorylation (RyR2-P) plays in this. Given the role of RyRs in elevating [Ca^{2+}]i and their potential as a target for AD treatment, this review will consolidate existing knowledge on how RyRs influence neuronal function under normal physiological circumstances and during the initiation of AD.

Employing a methodical strategy, a thorough literature search across three databases was conducted: Medline, Scopus, and Google Scholar, applying stringent criteria for selection to guarantee a comprehensive analysis, encompassing electrophysiological and molecular studies. Specifically, we included only *in vitro* or *in vivo* studies that investigated the impact of RyR2 dysfunction in Alzheimer's disease, intentionally excluding

computer modelling studies. This strategy was designed to encompass a broad spectrum of empirical research, providing a holistic analysis of RyR's role in AD pathology.

The rapid review synthesised findings from ten studies on RyR2's role in AD, revealing critical insights into the molecular underpinnings of the disease. The research collectively exhibits that modulation of RyR2 activity—through genetic, pharmacological, or biochemical means—holds significant therapeutic potential. Discrepancies in methodologies and outcomes underscore the complexity of RyR2's function in neuronal health and disease progression, advocating for a refined approach to targeting Ca^{2+} signalling pathways in Alzheimer's treatment strategies. RyR2-P, induced by beta-amyloid's interaction with beta-adrenergic receptors, leads to excessive Ca^{2+} release, disrupting intracellular Ca^{2+} balance. Research suggests this dysregulation indirectly influences Aβ production by affecting the activity of secretases involved in amyloid precursor protein (APP) processing and may impact tau pathology through mechanisms such as calpain activation, which can degrade proteins that regulate both Aβ and tau [4]. Additionally, elevated Ca^{2+} levels contribute to an environment that facilitates glycogen synthase kinase- β (GSK-3β) activity, promoting tau phosphorylation and aggregation. Simultaneously, Ca^{2+} overload impairs mitochondrial function, exacerbating neuronal damage through increased oxidative stress and energy deficits [5]. This perspective emphasises the complex role of Ca^{2+} signalling in Alzheimer's progression, highlighting its critical interactions. Key findings suggest targeting the RyR2-P could reduce synaptic dysfunction and Aβ production, offering a potential therapeutic strategy. Thus, therapeutic interventions that modulate RyR2 activity may halt or reverse AD symptoms.

To conclude, this synthesis highlights the need for a multi-targeted approach in AD treatment, spotlighting RyR2 as a candidate for targeted modulation, and specifically its phosphorylation, as key focuses for potential therapeutic intervention. This suggests a strategy that includes targeted modulation of RyR2-P among the approaches for future treatments. This would be necessary as there are no disease-modifying treatments for AD currently approved in the UK.

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Predicting Cell Entry Receptors for the Envelope Protein of Human Endogenous Retrovirus H (HERV-H)

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Human endogenous retroviruses (HERVs) are gene sequences originating from extinct viruses that infected host cells millions of years ago. They incorporated themselves into the human genome and continue to be passed down through generations[1,2]. To date, HERVs constitute approximately 8% of the human genome[1]. Although initially HERVs were characterized as latent DNA, they are now recognised to have the potential to express functional envelope proteins in certain cancer diseases as well as in physiological processes[1]. However, the mechanisms of action and the cell entry receptors that these envelope proteins bind to are yet to be determined[1,2]. One of these HERVs in particular, HERV-H, is commonly expressed in breast and lung cancer, and it is thought to have roles in cancer pathology and progression[2], yet the lack of structural information and knowledge of cellular receptor and tropism hinders much needed research on the subject. Therefore, the aim of this research project was to predict the cellular entry receptors that HERV-H envelope protein binds to and analyse how this could contribute to cancer pathology.

This research project aimed to provide a three-dimensional structure for the HERV-H envelope protein, starting from its amino acid sequence, by exploring both a protein threading and a homology modelling approach. The model developed was utilised to predict how relevant receptors might bind to HERV-H, using a protein-protein docking approach. The receptors included in this project were known receptors that mediated cell entry to

proteins with a similar amino acid sequence to HERV-H. The results of each docking simulation were analysed in terms of the predicted contacts between the envelope protein and each putative receptor, the predicted binding surface, and the docking score. These evaluations enabled the identification and ranking of likely cell entry receptors for HERV-H.

An initial model obtained for the HERV-H envelope protein constructed through a protein threading approach had to be discarded; instead, a suitable structure was obtained using a homology modelling technique. Syncytin-2, the envelope protein of the related retrovirus HERV-FRD, was identified as the most appropriate template to build the model, as it has 36.5% sequence identity with HERV-H[3]. This model was utilised in the protein-protein docking simulation with relevant receptors. The Alanine, Serine, Cysteine Transporter 2 (ASCT2) and the C-Type Lectin Domain Family 10 Member A (CLEC10A) were the cell entry receptors with the highest number of contacts to the HERV-H envelope.

The fact that ASCT2 had been identified as a likely cell entry receptor to the HERV-H envelope protein implicates that HERV-H protein could contribute to aiding tumour growth, by fulfilling metabolic demands of tumour cells[4]. Top predicted receptors for the HERV-H envelope identified in this research project will be expressed in suitable cell lines by virology collaborators, to then perform binding and cell entry experimental assays with HERV-H. These studies may elucidate the exact contribution of HERV-H to the progression of tumour growth, with the intention of supporting further developments in cancer treatments.

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An Exploratory Study Investigating Diazepam Poly-Drug Prescribing, Poisoning and Mortality Data in England and Wales 2017-2022

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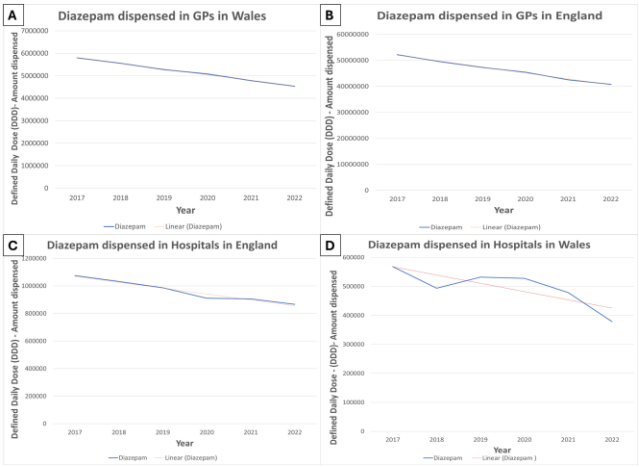
Benzodiazepines are licensed for treatment of anxiety, insomnia, and muscle spasms. They exert anxiolytic and sedative effects and are associated with risk of drug dependence and tolerance; and when taken in conjunction with other substances, the likelihood of toxicity increases. Due to the increased concerns around benzodiazepine use, restrictions have been implemented around prescribing benzodiazepines[1]. The study aims to provide a better understanding of the nature of diazepam use in England and Wales, forming the basis for subsequent research. No previous study has looked at these combinations of datasets in England and Wales in focus of diazepam polydrug use and during this timeframe.

Mortality rates were provided by the ONS from 2017-2021 (Office for National Statistics). Data for dispensed prescriptions in Primary and secondary care were collected for diazepam in England and Wales and was analysed using the Defined Daily Dose[2]. The UKPID dataset (United Kingdom Poisons Information Database) provided access to benzodiazepine poisoning enquiries made to the NPIS (National Poisons information service). Exclusion criteria was applied to the UKPID data to only show polydrug poisoning involving diazepam.

An overall decrease in diazepam prescribing was seen over the study period in England and Wales in both Primary and secondary care (Figure A1). Deaths where diazepam was mentioned on the death certificate contributed to 61.8% of all benzodiazepine-related deaths over the study period. UKPID enquiries showed a 9.2% decrease in diazepam polysubstance poisonings from 2017 to 2022. Intentional poisonings were significantly higher in female patients ($P < 0.05$) in contrast to males where recreational abuse was significantly higher ($P < 0.001$). The most common substances co-ingested with Diazepam included opioids, antidepressants, and alcohol. Moreover, there has been a 36.4% increase prevalence in non-prescribed diazepam use based on NPIS enquiries; Diazepam was obtained via buying online or abroad, on the ‘street’ or using another person’s prescribed diazepam.

Despite the overall decrease in prescribing of diazepam, there is still a slight increasing prevalence of poisonings and suicides associated with diazepam. The decrease in Diazepam prescribing is likely due to the 2011 MHRA reminder alert, which brought about prescribing restrictions, such as lowest effective dose for up to 2-4 weeks[1]. Illicit benzodiazepine have not only risen in England and Wales but also in Scotland where diazepam is one of the most common substances of abuse[2]. CNS depression and respiratory distress is a known risk when opioids are co-ingested with diazepam[3]. In terms of polypharmacy, diazepam has shown to interact with other substances although we cannot determine if diazepam is the true cause of poisonings. Nevertheless, increased public awareness and education around the use of diazepam is vital to guarantee patient safety.



Figure/Table A1: Six-year AWTTC Diazepam ' Defined Daily Dose' dispensing trends in primary and secondary care in England and Wales, 2017-2022.

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Do we have any viable alternatives to the ErbB receptors for targeting the cell membrane of breast cancer cells

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There have been limited advancement for drug treatments available for breast cancer (BC) despite globally being the second most leading cause of death in women. Chemotherapy is widely used for cancer patients however involves many toxic side effects due to its untargeted nature. Targeted therapy involves targeting specific receptors on cancer plasma membranes without harming normal body cells; Herceptin is a HER2 targeted therapy, which targets the HER2 receptor found extracellularly on the BC plasma membrane. However very few treatments other than those targeting the ErbB receptors have yet to be approved. Sacituzumab Govitecan has been the most recent antibody drug conjugate targeting the TROP2 transmembrane receptor approved for use by the Food and Drug Administration (FDA) [1]. By undergoing a rapid review of the literature, I hope to discover potential biomarkers on the plasma membrane of BC cells that can be successfully targeted to incorporate into future treatments.

A rapid review was conducted to assess the literature available for plasma membrane breast cancer targets through utilising the databases Scopus and Embase. The keywords searched were “monoclonal antibody”, “breast cancer” and “cell surface” which had generated journal articles exploring the use of plasma proteins as potential targets for further preclinical and clinical studies. Study trials sought from Clinicaltrials.gov was used to find that some plasma membrane targets have been in late phase clinical trials such as, VEGF-A and GP-NMB, targeted by monoclonal antibodies in phase 3 clinical trials. These clinical trials have been critically assessed for potential future biomarkers by comparing the measured endpoints to its comparator group.

There seems to be promising new targets other than the ErbB receptors found in clinical trials and in preclinical studies. The Ascent trial has shown to be a successful new plasma membrane target approved for use for "Participants with Refractory/Relapsed Metastatic Triple-Negative Breast Cancer." The results have shown prolonged PFS (progression free survival) compared to the active comparator group. Another plasma membrane target that has shown successful primary outcomes is the Ribbon-2 trial, targeting the VEGF-A plasma membrane receptor target with the monoclonal antibody Bevacizumab, results has shown increase in PFS and OS (overall survival) compared to the placebo group[2]. Many preclinical studies have been initiated for potential plasma membrane targets such as EphA10 which shown good clinical advances for future clinical trial study in human populations.[3]

In conclusion there are many alternatives to targeting the plasma membrane of breast cancer cells other than the ErbB family of receptors. However there needs to be more receptor targets from the literature brought into clinical trial studies to be tested in human population studies for patients with locally advanced or metastatic breast cancer as only a small number of studies have been implemented into human clinical trials. Furthermore, we need to see improvement in the number of completed trials published with results in clinical registers as some early phase trials have been completed with no results published or prematurely ended/terminated due to adverse toxicity to patients or ineffective clinical endpoints.[4]

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Is Supplementation with Commercially Available Lion's Mane Mushroom Products Effective in Preventing Alzheimer's Disease?

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Lion's Mane Mushroom, or Hericium erinaceus, is an edible mushroom that grows on hardwood trees and is native to North America, Europe, and Asia. It has a long history of use in traditional Chinese medicine, being used to replenish the spleen, strengthen the stomach, promote digestion, and strengthen brain activity. Today, products containing Lion's Mane Mushroom are widely available to buy online and in health stores. Supplementation with these products is claimed to prevent Alzheimer's Disease. As well as being an area of unmet clinical need (i.e. there is no cure), the prevalence of Alzheimer's disease will only increase as the population continues to age, so it is vital that products with activity against Alzheimer's Disease-related pathologies are investigated further. Current research into Lion's Mane Mushroom is being focussed on its secondary metabolites, particularly Erinacine A. It has been found to promote Nerve Growth Factor (NGF) biosynthesis in vitro[1], suggesting its potential value for the prevention of Alzheimer's Disease. This review therefore aims to establish the effect of Erinacine A on Alzheimer's Disease-related pathologies before using this data to establish whether any potential benefits of Erinacine A may be obtained from daily supplementation with commercially available Lion's Mane Mushroom products.

A rapid review approach was adopted. Databases Medline (Ovid), Scopus and Google Scholar were searched for 'Hericium erinaceus' AND 'Erinacine A' AND 'Alzheimer's Disease' OR 'Cognitive Impairment'. Studies were critically assessed using a CASP framework for randomised controlled trials and a modified CASP framework for experimental studies. Studies that measured the effect of Erinacine A on Alzheimer's disease-related pathologies were taken forward for further assessment. The disease model (patient/in vivo/in vitro) and mechanism of action of Erinacine A on relevant pathologies were extracted for further analysis.

Ten publications met inclusion/exclusion criteria and were taken forward for analysis. Of these, two publications were randomised controlled trials which offered valuable data on the effect of Erinacine A on Alzheimer's Disease and its important biomarkers in humans. One study used reported better performance in cognitive function tests and an attenuated rate of increase in amyloid-β levels in early Alzheimer's Disease patients[2], while another reported an attenuated rate of decline in neurotrophic factors such as NGF[3]. Six studies used mice as in vivo Alzheimer's Disease models, where Erinacine A improved cognitive and locomotor frailty index scores and reduced both the size and number of amyloid-β plaques[4]. Two other studies used in vitro models of Alzheimer's Disease, where Erinacine A protected cell viability in a dose dependent manner glutamate insult[5].

The data generated from this review provides direct evidence of the neuroprotective properties of Erinacine A and highlights its potential as a therapeutic for the prevention of Alzheimer's Disease. However, most of the studies used Erinacine A-enriched H. erinaceus as an intervention. Studies using Lion's Mane extract all used HPLC to quantify the amount of Erinacine A present, which often yielded very low concentrations. While these low doses of Erinacine A may be efficacious in animal models, it will likely require a much higher dose to replicate this effect in humans – a dose which is likely unachievable via supplementation with commercially available products, which often use Lion's Mane extract. This review therefore demonstrates the potential of Erinacine A as a therapeutic for the prevention of Alzheimer's Disease, however it is unlikely that these therapeutic effects can be achieved via supplementation with commercially available Lion's Mane Mushroom products.

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Do Gotu Kola Supplements Offer Neuroprotection and Cognitive Enhancement? A Systematic Approach

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Gotu Kola is a perennial herb native to tropical Asia that holds a historical place in Ayurveda and traditional Chinese medicine for its rejuvenating properties.[1] Despite a wealth of literature on dermatology, with comprehensive reviews available,[2] this study explores the claims surrounding Gotu Kola's neuroprotection and cognitive enhancement effects, focusing on its bioactive compounds, asiaticoside and asiatic acid.[1] Addressing a gap in current literature by using a systematic approach, this research aims to furnish evidence that either validates or challenges claims regarding the cognitive benefits associated with commercially available Gotu Kola supplements. This research aims to provide healthcare professionals with evidence-based information by examining both *in vitro* and *in vivo* methods to assess the efficacy of asiaticoside and asiatic acid in neuroprotection and cognitive enhancement. By scrutinising claims made by supplements on the market, it seeks to provide evidence that informs decisions regarding Gotu Kola's utilisation and recommendations for use.

A systematic approach was undertaken to gather relevant literature using a range of search terms including "Gotu Kola", *"Centella Asiatica"* and "Indian Pennywort" as well as utilising search terms such as "Neuro", "Psycho", "Brain", "Cognitive" and others, alongside Gotu Kola's bioactive compounds, "asiaticoside" and "asiatic acid". The search was conducted across multiple databases including Web of Science, Scopus, Emcare, Embase, and Medline, following PRISMA guidelines for article selection. Initially, the search yielded 702 papers from which a thorough screening process was conducted.

Within this research, 27 papers underwent analysis, investigating the cognitive enhancement and neuroprotective properties of asiaticoside and asiatic acid in Gotu Kola. Fifteen papers focused on *in vivo* models, seven studies on *in vitro* models, and four examined both models. A customised CASP checklist facilitated the inclusion of high-quality studies for the quantitative analysis, with the selected papers presenting with clear results supported by appropriate statistical analyses. *In vivo* models assessed memory and learning via behavioural tasks with two studies, Nasir *et al.*[3] and Sirichoat *et al.*[4], looking at the isolated effects of asiaticoside and asiatic acid showing cognitive enhancement potential. While Nasir MN *et al.,*[3] focused on asiaticoside impact on blood pressure dynamic and memory enhancement, Sirichoat *et al.*[4] investigated asiatic acid's role in spatial working memory and neurogenesis, both highlighting duration-dependent effects with dose treatment of 30mg/kg. Additionally, seven studies replicated ischemic conditions demonstrating

neuroprotective effects against oxidative stress, inflammation, and apoptosis, with maximum protection observed at 75mg/kg and showing significant improvements in memory and reductions in infarct volume. Most papers concentrated on neurodegenerative diseases, showing significant neuroprotective effects against various neurotoxic chemicals. *In vivo* models demonstrated improved behavioural outcomes, while *in vitro* studies reduced biological parameters, with 75mg/kg showing maximum protection.

Exploring Gotu Kola's asiaticoside and asiatic acid for cognitive enhancement and neuroprotection, this study aimed to assess the existing literature and provide evidence-based information for healthcare professionals. Across various experimental designs, significant improvements in memory and learning,[3,4] alongside neuroprotective effects such as mitigating inflammation, oxidative stress, and apoptosis were observed. While these biomarkers, provide measurable data, translating these findings into cognitive improvements and neuroprotection remains challenging. Behavioural methods were utilised to assess learning and memory, although subjective, arguably provide a more comprehensive and holistic interpretation of cognitive function. The debate over *in vivo* versus *in vitro* models raises questions about the most clinically relevant approach for assessing cognitive function. Higher doses of 75mg/kg provided maximum effect and protection, with no added benefit observed at doses exceeding this level, however the lack of clarity regarding dosing and the absence of regulation in Gotu Kola supplements pose challenges for healthcare professionals to make decisions. In conclusion, while evidence supports cognitive and neuroprotective effects, discrepancies in dosing guidelines and suggestions falling below those supported by scientific evidence, warrants caution. Healthcare professionals should therefore proceed with caution until supplements have the exact formulation and precise concentration of the bioactive components.

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Exploring the Stability of Polylactic Acid for Perfusion Cassettes used in Bio-Printed Skin Models

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Bio-printed skin models are three-dimensional constructs of human tissue. Bio-printing technology is utilised to create these models by depositing cells, like keratinocytes, layer-by-layer to replicate the structure and function of the epidermis[1]. To address the issue of vascularisation, a perfusion cassette is incorporated into bio-printed models. A perfusion cassette is a 3D-printed device that consists of a culture plate with integrated channels through which a nutrient-rich media can flow. By continuously perfusing media through the cassette, the bio-printed model receives a steady supply of nutrients and oxygen, whilst waste products are efficiently removed. This perfused construct will offer a more accurate physiological representation of the skin's epidermis when compared to traditional two-dimensional cell cultures in a petri dish, for example[2]. These systems are fundamental tools for advancing pharmaceutical applications such as drug development and toxicity testing. Polylactic acid (PLA) is a natural polymer that could be used to 3D print a perfusion cassette due to its biocompatibility and favourable properties for 3D printing[3,4]. Here, our study aims to assess the stability of PLA study when exposed to perfusion cassette conditions during bio-printing and cell culture. This will determine whether PLA is a suitable polymer to 3D-print a perfusion cassette to successfully vascularise a bio-printed model.

In this study, we designed, and 3D-printed PLA culture plate inserts to investigate the stability of the polymer under cell culture and bio-printing conditions. The PLA inserts were designed using computer-aided design software and tailored to fit a Corning™ Costar™ 6-well culture plate. The PLA inserts were incubated with either Dulbecco's Modified Eagle Medium (DMEM) or mineral oil to assess changes in stability. Mineral oil was used to simulate bio-printing conditions, while DMEM replicated standard cell culture conditions. Weight measurements and microscopy images of PLA inserts were taken before and after incubation to evaluate any changes in PLA mass or degradation of the polymer's integrity.

Various insert designs were tested, and each was modified until satisfied with both dimensions and infill pattern. Due to human error, there were discrepancies between insert sets where different infill patterns were selected in the 3D print process. There was a notable difference in print quality between both sets of inserts,

as well as their ability to contain media and oil through the period of incubation. Mass analysis revealed significant changes in insert mass after incubation with DMEM and mineral oil. Mineral oil caused visible distortion of PLA printed layers, whilst staining was present in those incubated with DMEM.

Results indicate that in the context of a perfusion cassette PLA is a stable polymer under bio-printing and cell-culture conditions. Whilst the polymer is stable, there are a few considerations to make when using PLA to 3D-print perfusion cassettes to vascularise bio-printed skin models. Mineral oil and DMEM induce an increase in mass and structural alterations in PLA, suggesting possible absorption and degradation in the polymer. Results must be applied to a perfusion cassette where there is limited contact time between PLA and mineral oil. Mineral oil is used as a temporary support system for bio-inks in the bio-printing process. The extent of oil-induced swelling in PLA may be lessened when considering its intended use. Further research is needed to understand media-PLA interactions, particularly with DMEM, to ensure there is no effect on perfusion capability in the device. Our study was limited as the volume of DMEM incubated with PLA did not accurately represent the volume of DMEM used in a perfusion cassette. Print quality significantly impacts PLA stability; variations in print quality affect the structural integrity of PLA and exacerbate media and oil absorption. Tight regulation of print quality and environment is critical for successful perfusion systems. Suboptimal prints compromise PLA's integrity causing potential issues within the cassette's functionality and nutrient distribution, possibly leading to unsuccessfully vascularised bio-printed epidermal models.

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Evaluation of the tools used to assess the impact of a homemade nutritional milkshake alternative to oral nutritional supplements in care homes

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Oral nutritional supplements (ONS) are widely prescribed drinks used to fortify diets with additional micronutrients and macronutrients[1]. Effectiveness is often dependent on compliance[2], which can be poor as many patients do not like the flavour of these drinks. This leads to increased risks of morbidity and mortality[3]. Therefore, to ensure that patients receive adequate nutrients in their diets, it is essential that alternatives to ONS are investigated. A fortified homemade milkshake (HMS) alternative to prescribed ONS is being trialled as a pilot project in five care homes in Hywel Dda University Health Board. This project aims to evaluate the current audit tool used to assess the impact of the pilot programme and to explore the perception of care homes and their residents on the switch, to ultimately inform the development of a further audit tool that can sufficiently capture the full impact of an extended roll out.

Quantitative data from the audit tool was analysed to determine whether there were changes in residents' weight, and qualitative data was analysed to understand the impact assessed by the tool. The insufficient data collected by the tool meant further investigation into the impact was required, to gather additional background on previous experiences with ONS and information on important parameters affected by HMS. An interview schedule using a semi-structured approach was designed, including questions on perceptions of care home staff and residents, and impact of the switch on these groups. Qualitative data from interviews was analysed thematically, coding into themes including staff's perspectives on the audit tool and residents' wellbeing, response of the residents and change in compliance, efficiency and convenience, and cost effectiveness.

Data collected by the audit tool showed that 53% of residents maintained stable weight after starting HMS, 29% gained weight and 18% lost weight. BMIs (body mass index) and MUST scores (malnutrition universal screening tool) are used to determine someone's malnutrition risk but were not recorded for all residents. Some information on co-morbidities and medications were recorded, with 22% of residents described as living with dementia or being cognitively impaired, which care staff said in interview hindered their ability to express an opinion on the change from ONS to HMS. Staff suggested including category of care in the audit tool, to allow for a better understanding of the impact of HMS on residents in relation to the goals of their care. Cost was a concern for the care homes, as the homes themselves have to pay for HMS instead of the NHS paying for ONS, however staff believe HMS is cost effective. Six interviews were conducted, involving eight members of

care staff from all five care homes - positive views were expressed about the switch from ONS to HMS, with four out of the five homes saying residents 'enjoyed' the milkshake and that compliance was improved. After switching from ONS to HMS all care homes said they had a reduction in number dietetic referrals made.

The data collected thus far is inconsistent, and the small sample size means there is insufficient evidence to make meaningful comparisons between use of HMS and ONS at this stage. Weights should be consistently collected, with clearly distinguished pre- and post-pilot weights. Along with this, BMI and MUST scores should be calculated to determine changes in residents' nutritional status. Malnutrition is linked to poor health outcomes and infection[4], so MAR charts (medication administration record chart} and nursing notes should be monitored using the audit tool to observe signs of pre-existing disease progression, new diagnoses, and recurring illness e.g., UTI and pressure ulcers. The positive anecdotal evidence from the interviewees and weight stability or gain seen from the audit tool in the majority of residents is supportive of the switch from ONS to HMS. Further monitoring of a larger sample size, for a longer period of time would be required in order to make an accurate assessment of the broader impact of the homemade milkshakes in care homes.

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The development of PROTACs for the treatment of Glioblastoma: Opportunities and challenges

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Glioblastoma (GBM) is one of the most aggressive cancers globally, with a median survival time of just 15 months, and devastatingly only 25% of patients survive one year after diagnosis[1,2]. Several factors contribute to a poor prognosis, such as the presence of drug resistant GBM stem like cells (GSCs) that favour tumour relapse, rapid progression, and invasion of the surrounding cells in the brain, with the blood brain barrier (BBB) tightly regulating the movement of substances into the brain making drug penetration difficult. The current gold standard treatment consists of the oral alkylating agent Temozolomide (TMZ), in conjunction with surgical removal of the tumour and radiotherapy, however this has provided limited success. Subsequently, new treatment approaches have been explored, including Proteolysis targeting chimeras (PROTACs), heterobifunctional molecules that break down unwanted proteins by simultaneously binding a protein of interest (POI) and E3 ligase, initiating protein degradation[3]. Their ability to target previously 'undruggable' proteins and to be used at lower concentrations make PROTACs desirable as new drug molecules[4]. Here, a rapid review considers the effectiveness of PROTACs against laboratory models of GBM while evaluating the challenges and limitations.

A rapid review was conducted, searching the databases Medline (Ovid), Embase (Ovid) and Scopus. The search terms included were;(Glioblastoma* OR GBM OR Glioblastoma Multiforme OR Brain tum*) AND (PROTAC* OR Proteolysis targeting chimera OR Ubiquitin Proteasome system). These various search terms along with comprehensive inclusion and exclusion criteria were used to identify relevant literature, extracting data relating to PROTACs and their effect against models of GBM. Studies were then assessed for their quality using a modified CASP checklist for pre-clinical studies. Additional literature was found using the snowballing technique, while supporting articles were identified through citations of relevant papers, as although they didn't meet the inclusion criteria, they contained useful information.

Seven pre-clinical studies were included in the final rapid review. Of these seven studies, all seven conducted in vitro studies examining the effect of PROTACs against human GBM cell lines, while five of the articles included in vivo studies, predominantly in xenograft mouse models. The PROTACs targeted various proteins, using different E3 ligase enzymes, and showed significant degradation of proteins in vitro as well as exerting anti-proliferative effects. In vivo, tumour growth was substantially inhibited by PROTACs, with tumour volume and weight decreasing and a survival benefit mediating in the mice. When compared to TMZ, a 3-fold reduction in tumour growth was seen when PROTACs were administered, underlining their huge potential. As well as this, none of the studies showed any obvious toxicity or side effects after administration with PROTACs, with

the weight of mice staying relatively unchanged, although in the highest doses precipitation of drug could be seen around vital organs.

Despite the clear opportunities PROTACs provide as a novel treatment approach, the absence of studies in humans make definitive conclusions on their prospect difficult. Xenograft mouse models can show good predictability, but don't fully mimic the complex environment found in humans, being immunocompromised to allow for the implantation of the relevant human tumour cells. Furthermore, arguably the biggest challenge PROTACs face in treating GBM is overcoming the BBB. Notably, the papers generally neglected this despite its importance, with only one paper evaluating how the drug can be optimised to penetrate the BBB. This study found that incorporating the drug into a nanoparticle increased protein degradation, tumour inhibition and enhanced bioavailability. Future studies are essential to examine both the efficacy and safety of PROTACs in humans, particularly when faced with the challenge of reaching the target site, while an effective strategy must be developed to accurately measure the outcomes of human studies, such as the use of biomarkers. Although in the early stages of development, with a great deal of work and further studies required, it is evident that PROTACs provide huge opportunities as a realistic treatment in combating this deadly disease.

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Determining the effect of varying charge content in cryogel scaffolds in relation to physical characteristics for their use as a delivery mechanism of de-myelinating agents to develop ex-vivo Multiple Sclerosis models

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Multiple sclerosis (MS) is an inflammatory disease of the central nervous system characterized by demyelination and neuronal damage, triggered by environmental factors in genetically predisposed individuals[1]. The primary pathophysiology of MS is demyelination of nerve fibres, causing disruptions of inter-cell signalling between neurons. It is challenging to treat with no cure available. Accurate models reflecting MS pathophysiology are crucial for research, prompting the development of ex-vivo models using 'slice culture systems'. However, original slice culture models were based on global demyelination of tissue samples. Whereas, in MS, small pockets of localised demyelination are formed. Researchers introduced cryogel scaffolds to address this issue, enabling precise delivery of demyelinating agents to specific regions, thus, accurately recreating MS pathophysiology[2]. Cryogel scaffolds were initially composed solely of PEGDA, however, these scaffolds caused tissue damage when placed on tissue samples. The incorporation of SPA (a negatively charged monomer) prevented adhesion and thus, avoided damage[3]. The characteristics of scaffolds composed of PEGDA and SPA are unknown meaning they are not being used at their full efficacy. Characterisation of the cryogel scaffolds will allow future researchers to optimise properties to suit their projects.

In this project the physical characteristics of the cryogel scaffolds were studied by completing lab based primary research. Several experiments including, uniaxial compression, swelling measurements and dye loading profiles were undertaken in addition to light, widefield and confocal microscopy. With the aim to fully characterise the cryogels.

Fourier Transform Infrared Spectroscopy (FTIR) was used to confirm complete crosslinking and see qualitatively if more SPA was incorporated in the polymer. The swelling ratio of cryogel scaffolds, as determined through both microscopy and calliper gauge analysis, demonstrated an increase with higher SPA content which could be utilized to customize cryogel size and the area of focal demyelination. Loading capabilities of the cryogels were tested using three differently charged fluorescent dyes. Eosin-Y (negative), BODIPY (zwitterion) and Di(I) (positive). BODIPY, and Eosin-Y loading showed minimal change with SPA content whilst Di(I) loading increased with higher SPA content. These results allow for optimisation of agent loading when using a positive agent however, there is limited customisability with zwitterionic loading as it is time independent. One limitation with the loading data is that concentrations of dye used in this project are significantly lower than concentrations used in research. Uniaxial compression analysis revealed that cryogels became softer with elevated SPA content, measured as a decreased Young's modulus. This adjustability may

allow a better biocompatibility of cryogels on soft brain tissue. However, higher SPA levels may compromise cryogel durability, impacting handling. Microscopy results depicted less insightful structural changes with increasing SPA content with random pore structure formation, however this did depict dye loading in both the pores and on the struts of the cryogel scaffold structure.

The results found clear evidence that the characteristics of the cryogel scaffolds can be varied to suit the individual needs of researchers. This paper serves as a good foundation into the analysis of the cryogel characteristics and allows these properties to be used moving forward with current research. Allowing improved experimental methods to support the development of novel remyelinating therapeutics. With more time this research project would be able to examine more characteristics such as pore size and membrane release data which, whilst not essential, is useful for further understanding of the cryogels.

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Exploring the economic and operational impact and views of Community Pharmacists of prescribing ESA medication on WP10HP prescriptions for people with chronic kidney disease across South West Wales

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Erythropoiesis stimulating agents (ESAs) are an exogenous source of the glycoprotein erythropoietin (EPO), used in the treatment of anaemia of chronic kidney disease (CKD)[1]. Patients with CKD have reduced renal EPO production and consequently the bone marrow isn't stimulated enough to produce sufficient numbers of red blood cells[2], leading to reduced oxygen transport around the body. Therefore, ESAs are given to patients, often via a subcutaneous injection[3], with the aim of reaching target haemoglobin levels of 100-120g/L[3] and reducing symptoms of anaemia. Recently, there has been a proposal by South West Wales Renal Department (SWW-RD) to add ESAs to a primary care rebate scheme, allowing prescribing of ESAs on a WP10HP prescription for dispensing in a community pharmacy as opposed to in hospital. This new method of dispensing provides an opportunity for cost savings as prescriptions in community pharmacies are VAT reclaimable whereas the VAT associated with hospital dispensing is non recoverable[4]. Following the proposal this project seeks to evaluate the potential cost and operational implications this could have, with a particular focus on the impact on community pharmacies and pharmacists.

Two types of methodologies were used in this project. Firstly, quantitative analysis of patient prescribing data was used to assess the number of people this scheme may impact on, while potential cost savings to the NHS budget were also considered. Secondly, after attaining ethical approval, a qualitative thematic analysis of data collected from a focus group of community pharmacists was undertaken to identify a key stakeholders view on the proposed change in prescribing practice. Using manual coding, all themes were identified through inductive methodology.

A total of 356 patients met the inclusion criteria for being potentially eligible for the new method of prescribing and dispensing of their ESA medication, of which 23.6% received homecare deliveries. On average, patients currently collecting from a renal clinic (n=272) would reduce their distance travelled by 21.46 miles if collecting from their local community pharmacy. The potential for financial savings for SWW-RD were apparent and estimated at £18,396 per annum for this defined cohort. Six participants were included in the pharmacist focus group and in total, four core themes emerged. These were: 1) Lack of Knowledge around ESA's & Training Required, 2) Risk associated with dispensing ESAs in the community 3) Storage & Delivery of ESAs and 4) Cost Implications for Pharmacy dispensing the ESA. There was a strong consensus amongst participants that part of the cost savings incurred within secondary care should be transferable to the community setting. Further sub-themes were also evident in the discussion.

The proposed scheme was perceived to be a positive change for patients, particularly those geographically isolated that travel large distances to clinic. Data highlights that a reduction in home-care delivery fees and drug expenditure would lead to cost savings for Renal Departments. However, foreseen challenges from

participants (in relation to limited knowledge around ESAs, delivery of cold chain items and cash flow) suggests further work is required to make this a viable switch into community pharmacy. Many of these concerns could be mitigated through the addition of a service alongside dispensing of the ESA, offering an opportunity for community pharmacy to add value whilst providing patient-centred healthcare. Overall, the findings can be utilised to support successful implementation of this proposal. Future research should focus on exploring the views of all stakeholders of this change to ensure patient satisfaction and treatment remains optimal alongside investigating the financial impact on all services involved.

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Washing practices and the effect of residual interfering substances on the performance of photocatalytic antimicrobial textiles

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Period poverty affects approximately 500 million women world-wide, these menstruating women and girls do not have access to safe menstruation management materials. These individuals are forced to use unhygienic means to manage their menstruation, giving rise to the risk of contracting serious genitourinary tract infections[1]. Cardiff University researchers[2] have been developing reusable sanitary pads coated in a metal oxide semiconductor with antimicrobial photocatalyst properties. This study investigated the impact of interfering substances on the biocidal effects of the metal oxide semiconductors, as well as the most optimal washing technique for the product to ensure optimal biocidal functioning.

Experimental data was collected analysing the antimicrobial efficacy of the four metal oxide semiconductors (photocatalysts A-D) against Escherichia coli in the presence of interfering substances haemoglobin (Hb) and synthetic vaginal fluid (SVF) at both pH 4.6 and pH 7 with exposure to the solar simulator over 2 set time points (2 and 4 hours). Data was collected by a process of enumeration, through the counting of colony forming units in a dilution series. A series of five different washing tests were carried out, 4 of which were based on the AATCC 61a accelerated washfastness test, on samples inoculated with Hb and the outcome of which was analysed using the alkaline haemitin assay.

At study inception, our results showed that photocatalyst A performed the most consistently across both time points and at all concentrations of Hb. At nearly all concentrations of Hb, photocatalyst A produced an over 4 $\log_{10}$ reduction at both 2 and 4 hours. Photocatalyst C performed better at 4 hours exposure in comparison to 2 hours, performance increased as the Hb concentrations decreased, producing just below a 4 $\log_{10}$ reduction at 1.17g/L of Hb. Photocatalyst D performed best at 2 hours exposure, and similarly to photocatalyst C, performed best at the lowest concentration of Hb but still did not reduce E. coli viability to below the lower limit of detection. Photocatalyst B was the least effective of the four, producing negative $\log_{10}$ reductions in E. coli viability after 2 hours exposure. Photocatalyst A was tested in the presence of SVF, it produced a 4 $\log_{10}$ reduction at both pH, demonstrating that SVF does not negatively impact the photocatalyst. The washing tests revealed that, for fabric coated with photocatalyst A, soaking in water for 1 hour would be a suitable way to wash the product as it reduces the level of residual Hb to below that at which we know the photocatalyst works.

The data suggests that Hb negatively impacts the performance of the photocatalysts. With photocatalyst A being the exception, as it showed to work consistently at all tested concentrations of Hb. As we know that photocatalyst A is functional at all tested concentrations of Hb, soaking in water for 1 hour should be recommended to users as the most appropriate washing technique. Moreover, further experimentation completed by others working on this project revealed that washing with detergent/soap can affect the integrity of the coating. More experimentation needs to be carried out to assess how repeated washing affects the performance of the photocatalysts, as well as how different weather conditions will affect the performance of the product when used in in-situ. Currently, antimicrobial textile testing standards do not require textiles to demonstrate efficacy in the presence of interfering substances, this may account for the discrepancies observed between antimicrobial textiles in testing and in situ[3].

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Progress and Challenges of Combination Therapy targeting Candida auris: A Rapid Review

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Candida auris (C. auris) is a fungus which has caused invasive infections worldwide as it can enter the bloodstream[1]. C. auris, was identified in 2009[2] and has caused many mortalities in patients, especially to those who are immunocompromised, in hospital and intensive care units. Managing C. auris infections presents a challenge, primarily because of its propensity to develop resistance against key antifungal drug classes[1], making treatment very difficult. Novel drugs can take years to research and have high costs; therefore it is important to use other approaches to try and overcome these infections. Combination therapy, where two or more drugs with different mechanisms of action, have been used successfully against other microbials and is thought to be a good approach to overcoming resistance. Using drugs that have already been approved and are safe to use in humans, allows less cost and time to find a successful treatment against C. auris. Therefore, this review will overview the combination therapies targeting C. auris.

A rapid review of the literature was conducted for this research by a single researcher. The key terms and deviations were ‘Candida auris’ OR ‘C. auris’ AND ‘combination’ OR ‘combined’ OR ‘synergic’ OR ‘synergistic’ AND ‘treatment’ OR ‘therapy’ OR ‘therapeutics’ OR ‘regimen’. The databases used were Scopus, PubMed and EMBASE. The papers were narrowed down to find relevant studies where only papers used were in the English language, written in the last 10 years and where one of the drugs tested in combination was an antifungal drug. Any papers where the treatment was targeting biofilms of C. auris, were excluded. The studies were critically analysed by using the `QUIN’ tool for in vitro studies.

After reviewing titles and abstracts, fifteen articles were included in the final review and they all tested combination therapy in vitro. Of these, six papers further evaluated combinations in vivo, where the in vitro analysis had shown promising results. In total, 52 combinations were analysed in this review, including an antifungal drug with: another antifungal, antibacterial, antivirals, antileishmanial, repurposed drugs and others such as natural peptides. Importantly, synergy was found in combination against over half of the clinical isolates tested in 62% of two antifungals, 67% of an antifungal with an antibacterial, 58% of antifungal with antivirals, 0% when an antifungal was tested with an antileishmanial, 56% of antifungal with repurposed drugs and 30% of antifungal with others. Synergy was assessed in most of these articles by calculating the fractional inhibitory concentration index (FICI), where the minimum inhibitory concentration (MIC) was used to evaluate how well the combinations work together. Itraconazole combined with antiviral agent lopinavir showed the most promising results, with two separate studies showing 100% synergy in vitro, and promising in vivo data, in both Caenorhabditis elegans and a mouse model[3,4]. Other combinations that showed 100% synergy in vitro included amphotericin B with anidulafungin, micafungin with voriconazole and saquinavir with itraconazole.

The combination of itraconazole with lopinavir showed significant findings, it is important to note that these findings included in vivo experiments as well, unlike some of the other combinations, which were only assessed in vitro. The combinations of drugs that seemed to work give us hope for further study, but for the purpose of this review, it is difficult to directly compare the results due to some inconsistencies. The combinations in the studies, were tested against different strains of C. auris, therefore the resistance and susceptibility may differ between experiments. Most studies were more comparable as they used the FICI to measure synergy, but some did not. This review shows some promising data, which now should be experimented at the next step in vivo or in humans, with certain combination therapies more likely to have clinical benefits than others. Despite these in vitro studies and early in vivo studies being a vital part of research in this area, they are only in the pre-clinical stage, therefore would need to be assessed further to see if the favourable combinations will actually be of any benefit to treating invasive C. auris infections in humans.

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Comparative analysis of the role of TMPRSS2 in the uptake of SARS-CoV-2 and Influenza A viruses

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SARS-CoV-2 and Influenza A (IAV) are both highly infectious viruses that contain class one fusion proteins on their surface that are activated upon cleavage; SARS-CoV-2 contains the Spike (S) protein and Influenza A contains Haemagglutinin (HA)[1]. Upon cleavage these fusion proteins facilitate the entry of the viruses into human cells and both viruses are known to enter cells via clathrin mediated endocytosis[1]. Studies show that the Transmembrane Serine Protease (TMPRSS2), which is found in the cellular membrane of endothelial cells[2] facilitates the endosomal uptake of IAV into cells by targeting HA. It is also known to target the SARS-CoV-2 S protein, therefore it is possible to hypothesise that TMPRSS2 should also facilitate the endosomal uptake of SARS-CoV-2 through the activation of the S protein. However, recent studies have shown that TMPRSS2 can also play a role in the uptake of SARS-CoV-2 through plasma membrane fusion[3]. This review will compare the effect TMPRSS2 has on both fusion proteins in order to understand how TMPRSS2 facilitates the uptake of SARS-CoV-2 via plasma membrane fusion.

A rapid review was conducted and the databases Medline (Ovid) and Scopus were used to gather experimental literature for this review. The databases were searched between (1/11/23 - 1/12/23) using the key words “SARS-CoV-2” OR “Influenza A” AND “TMPRSS2” AND “Spike Protein” OR “Haemagglutinin” AND “membrane fusion” OR “endosome”. An exclusion and inclusion criteria specified that all papers should be selected from 2019 onwards for SARS-CoV-2 due to it being such a novel virus and 2012 onwards for Influenza A which had been around for much longer and more widely researched. Studies were selected using the CASP model. All the studies selected had conducted experiments to report the role of TMPRSS2 in the uptake of SARS-CoV-2, or Influenza A and the uptake pathway that is followed in the presence of TMPRSS2. All studies had conducted their experiments in vitro and results were collected regarding the type of cell model used.

Eight papers were chosen focusing on SARS-CoV-2 and eight focusing on IAV. All papers used high quality cellular models to confirm that the presence of TMPRSS2 increased the uptake of both viruses into cells. One of the papers did not go into any further detail, however all the remaining papers confirmed that TMPRSS2 specifically targeted the Spike (S) Protein in SARS-CoV-2 and HA in IAV. Results from the papers showed that TMPRSS2 possibly cleaves HA at the HA0 monobasic cleavage site into the active HA1 HA2 subunits that are connected by a disulphide bond(2). In contrast, results for SARS-CoV-2 show that TMPRSS2 cleaves the Spike (S) protein at the S2 subunit which is already an active subunit, showing a clear difference between how TMPRSS2 cleaves both fusion proteins(4). It is also important to note that Haemagglutinin contains a monobasic cleavage site whilst the spike protein contains polybasic cleavage sites(2). Another discovery found when comparing the papers was that TMPRSS2 cleaved the Spike S protein the cell surface whilst it was found to cleave HA intracellularly(2-3). This could be a reason that SARS-CoV-2 can enter cells via the membrane surface, whilst IAV enters the cell via the endosomal pathway only. Two studies confirmed that TMPRSS2 played an active role in the uptake of SARS-CoV-2 via plasma membrane fusion as well as facilitating early endosomal uptake(3-4), whilst there was no evidence of IAV entering the cell via plasma membrane fusion(2). However from the studies it seems that for both viruses TMPRSS2 relies on an acidic pH for the uptake of the virus regardless of the uptake pathway followed by the virus.

It is clear TMPRSS2 plays an important role in the uptake of both viruses under acidic conditions. By comparing the action of TMPRSS2 on the Spike (S) Protein to HA it is possible to see how TMPRSS2 could play an additional role in the uptake of SARS-CoV-2 via plasma membrane fusion. This makes TMPRSS2 a viable drug target to reduce SARS-CoV-2 infections. However more research needs to be conducted due to limited in vivo evidence.

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What influences change in cardiac ryanodine receptor cluster organisation and what does this mean for calcium release?

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Cardiac ryanodine receptors (RyR2s), situated on the cardiomyocyte sarcoplasmic reticulum (SR)[1], are calcium (Ca^{2+}) release channels, which play a pivotal role in the maintenance of intracellular cardiomyocyte Ca^{2+} signalling, regulating the process of excitation-contraction coupling (ECC) (4). RyR2 channels exhibit a propensity to form clusters in a variety of sizes and shapes and coalesce into regular “quasi-crystalline” arrays, the function of this is believed to be the facilitation of inter-RyR communication, enabling synchronisation of Ca^{2+} release and termination, but this has not been unequivocally proven (6). The significance of these clusters deepens in interest when changes in cluster organisation are implicated in conditions such as, heart failure (HF), catecholaminergic polymorphic ventricular tachycardia (CPVT) and atrial fibrillation (AF)[2], suggesting a correlation between RyR2 clustering and the aetiology of cardiovascular diseases (CVDs). Defective phosphorylation is also implicated in the pathological mechanisms of said diseases, suggesting a link between the two phenomena.[1]

This project took the form of a rapid review. Scopus, PubMed and Embase databases were used to conduct searches with key terms being ‘Ryanodine receptor’ OR ‘RyR2’ AND ‘clustering’ or ‘grouping’ AND ‘Phosphorylation’ or ‘Pathology’. An excel sheet summarising all 140 papers was composed, where each title was analysed carefully to ensure relevance, which left 25 papers. Abstracts were subsequently scrutinised for relevance to the research question, leaving 9 papers to critically analyse.

Phosphorylation was identified to have an impact on cluster size, resulting in larger fragmented clusters[1,2], this fragmentation was shown to cause diastolic SR Ca^{2+} leak, potentially triggering arrythmia[2]. Phosphorylation by calmodulin dependent kinase (CaMKII – upregulated by adrenergic drive) was shown to promote cluster fragmentation, which was reversed upon inhibition of this kinase[6]. CaMKII phosphorylation also led to a reduced activation of Ca^{2+} sparks by cytosolic Ca^{2+} resulting in reduced fidelity of Ca^{2+}-induced Ca^{2+} release[6]. Auxiliary proteins were also of interest, where FKBP12.6, an accessory protein, binding of which is thought to stabilise the closed state of the channel,[1] dissociates from RyR2 when it is phosphorylated. When saturated with high concentrations of FKBP12.6, a reduction in SR Ca^{2+} release was apparent[1], also having an effect on the side-by-side distribution of the channels, directly resulting in a decrease in fidelity of a Ca^{2+} spark. Another RyR2 binding protein, junctophilin-2 (JPH2) was observed to localise in the central regions of the clusters (3), underlining it’s significance in maintaining cluster morphology. RyR2 clusters in a rat heart failure model appeared fragmented and smaller in size (5), resulting in more variable Ca^{2+} sparks produced, generating Ca^{2+} leak, which coincided with an increase in channel phosphorylation.

This research identified that changes in cluster formation can be due to multiple factors, but the most consistent reported is phosphorylation. This research also sheds light on the possible implications of RyR2 clustering and the role of accessory proteins and how this might impact cluster organisation. Understanding the mechanisms maintaining functional Ca^{2+} release and how developing targeted therapeutics in reversing the implications of phosphorylation or aberrant accessory protein binding in pathology could successfully reverse future morbidities and aid in the development of future diagnostic techniques.

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Engagement of higher education institutions with rural Welsh schools: Is there room for improvement?

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Although many students attend higher education in the UK, there are varying degrees of accessibility depending on factors including area, wealth, and background[1]. Due to lack of equal accessibility into higher education, certain minority groups in the population are under-represented at university. Students from rural Welsh areas are one of these groups who may not find higher education accessible to them, contributed to by the lack of successful widening access to higher education strategies for rural Welsh students. This is reflected in the lack of healthcare practitioners in Welsh rural areas, for example the Aneurin Bevan University Local Health Board only having 1 Welsh speaking GP per 20,000 of the population in 2018[2]. Many students decide after higher education, to return to their hometowns for work and to live. By widening access to higher education for those in rural Welsh areas wanting to study healthcare, it will help increase the number of healthcare professionals in rural Welsh areas when these students return after university[3].

The research aims to collect qualitative data by interviewing teachers about their experiences and opinions on their relationships with higher education establishments, exploring strategies that could improve these relationships. Hence, participant inclusion criteria consisted of preferably science teachers working in rural Welsh secondary schools or colleges. Exclusion criteria consisted of anyone who did not fit the inclusion criteria, as inclusion criteria had to be strict for a non-probability sample. Interview transcripts then underwent thematic analysis and were compared with findings from the background literature search. The Medline (Ovid) database was searched, and the appropriate literature was used to inform the interview schedule, the data collection tool used in this research.

Online interviews via MS Teams were held with six participants who met the inclusion criteria. Participants provided qualitative data regarding their relationships with higher education institutions (HEIs). On thematic analysis of interview transcripts, common ‘codes’ raised by participants were highlighted and then further combined to form sub-themes and larger themes. Some main themes uncovered were, location; the value of face-to-face on-campus visits and workshops, with these experiences described as more “memorable” for students. Sub-themes within this are delivery location and proximity affecting attendance of students at university open days, as students living further away may find it harder to attend. Another theme is that teachers lack knowledge and understanding of the courses offered by HEIs. Sub-themes within this are progression pathways and curriculum alignment between schools and HEIs. Relationships also presented as a main theme in this research, contributed to by the sub-themes of alumni with the value of these pre-existing links and the relationship between the student and the institution.

In conclusion, participants acknowledged their relationships with HEIs could be improved and participants showed desire to improve relationships with HEIs. Participants appreciate all widening access efforts with participant 3 stating, “Everything has its value…There’s nothing really that’s been not worth it.”, suggesting responsibility falls on HEIs to reach out to schools, because as found in this research, teachers find it difficult to contact HEIs. Widening access to HEIs for rural Welsh students can be improved by the following strategies. Strategies include contacts for teachers to HEIs to provide them with necessary information, as well as workshops and on-campus visits to universities via funded transport for students to see campuses and ask questions on-site. Also, having current university students who are alumni, visit schools to share their experience and explore potential “non-traditional” routes of accessing careers, providing some knowledge teachers may lack. Curriculum alignment between schools and HEIs was also suggested, linking schoolwork with career opportunities, as well as HEI-hosted summer schools which receive good student engagement.

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Evidence and significance of Pyk2 being a major player in the development of colorectal cancer and its metastasis

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Cancer is a major cause of death in developed countries. Most cancers kill by metastasis, their spread to other areas in the body. Colorectal cancer is the third most common malignant disease in humans and is very aggressive. In up to 70% of cases patients with colorectal cancer will develop secondary hepatic cancers due to the enterohepatic circulation. The liver can regenerate, and so metastases of this organ can be cured by resection provided the number, size and the location of the secondary growths allow it. Conventional chemotherapy can reduce the size of secondaries but often cause severe liver damage[1]. The remnant liver is unable to regenerate. Currently there is much interest in treating cancers with tyrosine kinase inhibitors as these agents appear less toxic. Tyrosine kinase inhibitors have provided a complete cure for some blood cancers but have a more modest effect in the treatment of solid tumours[2]. The non-receptor tyrosine kinase, Pyk2, is increased in all the major cancers[3]. Here, a rapid review was carried out to investigate its possible role in colorectal cancer and its metastasis. This could establish Pyk2 as a therapeutic target.

The rapid review used EMBASE (ovid), Medline (ovid), PubMed and Scopus databases. The search terms included Pyk2 and its synonyms; colorectal and alternative terminology; cancer and matched terms; and metastasis. Preliminary searches revealed that research on Pyk2 and colorectal cancer is a recent development[4]. This led to the use of a broad inclusive approach. Retrieved papers were judged critically using a modified CASP technique. Papers were identified from the above databases that could not be reviewed themselves, due to falling outside the inclusion criteria, but provided strong supporting evidence for the reviewed papers.

Nine publications obeyed inclusion/exclusion criteria and were then fully analysed. The levels of Pyk2 were increased by transfection and reduced by knockdown or the use of inhibitors. Taken together the results of the papers showed that Pyk2 increases the size of both primary colorectal and secondary hepatic growths at the same time as causing metastasis. Different experimental systems enabled this to be demonstrated both in vitro and in vivo. The mechanisms involved were highlighted by dividing the papers into three different areas. The first was the establishment of colorectal cancer (initiation, progression and survival), the second dealt with its metastasis while the third considered possible therapeutic interventions. The numbers of papers in each of these classes were roughly equivalent. In initiation, Pyk2 was involved in Wnt activation. In progression Pyk2 decreased autophagy and apoptosis and increased tumour oxidative phosphorylation. Pyk2 influenced survival by transferring monocytes/macrophages to the tumour microenvironment where they are converted to immunosuppressive cells. The role of Pyk2 in metastasis included its weakening of tight junctions, causing the secretion of proteolytic enzymes and disappearing on tumour cell detachment.

Evidence shows that Pyk2 has a role in many steps in the development of colorectal cancer. Its inhibition could slow or stop the process by more than one mechanism, making it a high value therapeutic target. Knockdown in vitro definitively showed Pyk2 involvement and does so in vivo in experimental mouse models. However, for clinical use in humans, only inhibitors are possible. Here there is ambiguity since current inhibitors stop the function of not only Pyk2 but also FAK (the other focal adhesion family member). This means that an observed result using these inhibitors cannot definitely show Pyk2 is responsible for an alleviating effect. The observed action may be mediated by FAK and therefore overestimate the importance of Pyk2. Clinically, dual inhibition may be desirable since in many cases inhibition of FAK causes a compensatory increase in Pyk2, overriding the therapy. The second generation, dual inhibitor defactinib has an acceptable safety profile, tolerability, stabilises even advanced colorectal cancers and is not associated with liver damage. The papers analysed in this rapid review suggest that inhibition of Pyk2 could modify all aspects of colorectal cancer ranging from preventing the cancer occurring in some patients with ulcerative colitis to increasing the efficacy of secondary hepatic cancer treatment by surgical resection, at the other extreme.

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Effects of Hormonal Replacement Therapy (HRT) on menopausal cancer survivors: Is it safe enough for prescription?

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The hormonal changes associated with the menopause can have marked effects on women's sexual and cardiovascular functions[1], mood and subsequently, their quality of life. Hormone Replacement Therapy (HRT) can help with controlling these unfavourable symptoms. However, the 2002 Women's Health Initiative Study[2], reported a link between an increased risk of cancer and HRT use. This finding expedited a reluctance in doctors worldwide to prescribe HRT and has proved to be a significant barrier for women with historic cancer to gain access to this treatment. In the UK, HRT is not available to women with previous cancer diagnoses[3]. Many women experience a premature or iatrogenic menopause as a consequence of their cancer therapy[4], often times, leaving them with unbearable symptoms on top of those due to their cancer. There is also a whole population of women who have had a childhood cancer and are now in remission, yet still being denied HRT. This problem will only continue to grow with time as the number of women surviving their cancers is on the rise[4] with improved treatments. The aim of this review is to address the research question in order to learn whether there really is a problem with the effects of HRT when given to female cancer survivors, focussing on its effects in terms of cancer recurrence, survival and mortality and whether any new prospective studies have been conducted to independently confirm the increased risk of cancer reported in 2002.

A rapid review was conducted to tackle the research question. Medline (Ovid), Embase (Ovid) and Scopus were the three databases in which a literature search was conducted for relevant articles, after having identified search terms. A PRISMA diagram detailing the numbers during the selection process can be found in the Supplementary Information section. All titles and abstracts were scanned to get the appropriate papers and those deemed fitting in accordance with the inclusion/exclusion criteria were read in full. Those were studies conducted on women with a history of cancer and treatment with HRT for the menopause. This narrowed down the selection of papers even more leaving only 11 papers that fitted the criteria for this review. The remaining papers were analysed and interpreted, focusing on the data that related to cancer recurrence, survival and mortality.

Across the 11 included papers, four different cancers were looked at. 7 papers looked at breast cancer, 1 at cervical adenocarcinoma, 3 at ovarian cancer and 1 at endometrial cancer. The current findings from these papers suggest that when HRT is given to female cancer survivors, the risk of cancer recurrences or death is lower or not significantly different to those of women not taking HRT, and has in some studies actually shown to improve the survival of these patients.

Contrary to the current notion that past cancer diagnoses should be a clear contraindication for HRT, the results from the available studies do not support the conclusion that HRT increases the risk of cancer recurrence or mortality.

However, all of the newer studies are observational in nature and include a relatively small number of patients. Despite this, the results reported show promise and provide hope for a reformation of the current HRT guidelines. Nonetheless, the preliminary nature of these studies mean that the findings cannot be substantiated without carrying out further studies in larger patient populations to demonstrate that the results are reproducible. This subgroup of patients should not continue to be denied HRT because of a mixture of fear and confusion coming from a small (and some may say inadequate) base of evidence and lack of understanding. Research needs to properly address this issue which significantly impacts their quality of life.

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Is activation of the cGAS-STING pathway in microglia a potential therapeutic target for ALS?

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Amyotrophic lateral sclerosis (ALS) is a devastating, progressive neurodegenerative disease characterised by loss of both upper and lower motor neurons resulting in paralysis and eventually death.[1] The underlying pathology is still unknown, however, discoveries in genetic mutations associated with this disease have advanced, two of these mutations being TDP-43 and SOD-1 among a multitude of others.[2] A hallmark feature of all neurodegenerative diseases is neuroinflammation via the release of interferon and other pro-inflammatory cytokines.[1] Emerging research has discovered that the cGAS-STING pathway may be overactivated in neurodegeneration to cause this neuroinflammation.[3] This pathway is present in microglia cells of the CNS and is triggered by dsDNA which can accumulate in the cytosol of cells due to mitochondrial damage.[4] This results in release of its own mtDNA into the cytosol of cells to activate cGAS and cause the downstream pathway to promote inflammation. New research has led to the discovery that misfolded protein aggregates of ALS can cause mitochondrial dysfunction.[3] ALS linked misfolded protein aggregation, mitochondrial damage, cGAS-STING overactivation and neuroinflammation ascertains a possible novel target for ALS.

A scoping literature review was conducted using the Scopus and Medline via Ovid databases and the search terms ‘amyotrophic lateral sclerosis’, ‘cGAS’ and ‘STING’. After critical analysis of the results, 3 papers were selected to be included in this review.

Mutations in TDP-43 gene, resulting in its accumulation in cells, is a hallmark of most ALS cases. It is known to localise in the cytoplasm of cells; however, it was theorised that it may also accumulate in the mitochondria causing mitochondrial dysfunction and hence release of mtDNA. Yu et al proved this theory by demonstrating that deletion of a subunit of TIM22 (membrane translocase responsible for TDP-43 to enter the mitochondria) results in no release of mtDNA into the cytoplasm.[3] Moreover, TDP-43 overexpression was also shown to cause mitochondrial dysfunction in these cells.[3] To analyse the link between ALS mutations and cGAS-STING pathway, molecules directly involved or downstream of this pathway were investigated. cGAMP, the molecule activated by cGAS, levels were elevated in sporadic type ALS tissues compared to control.[3] Downstream of this pathway is the release of pro-inflammatory molecules such as IFN-1 and NF-$_K$B which Yu et al showed they were both upregulated in ALS^{MUT} TDP-43 mouse neuronal cells compared to WT.[3] Ferecsko et al discovered that ALS cells with proteinopathies were highly STING immunopositive and were localised in close association to microglia.[4] Overactivation of cGAS or STING may be the driving force of this neuroinflammation, hence STING deletion in SOD-1-G93A mice in vivo showed increased survival and improved motor functions as well as STING deletion in TDP-43 murine mouse models of ALS showed a slowing in progression of the disease by 58%.[1,3] In order to move this theory towards a therapeutic approach, use of STING and cGAS inhibitors were employed. The cGAS and STING inhibitors, RU.521 and C-176 respectively, showed weight gain, motor improvement and increased survival periods in SOD-1-G93A mice.[1] Another STING inhibitor, H-151, in Prp-TDP-$43^{Tg/+}$ mice again showed improved motor function and prevention of excess motor neuron death.[3]

The cGAS-STING pathway is a major part of the neuroinflammatory response of the CNS, however, overstimulation of this pathway could be detrimental to cells of the CNS. TDP-43 and SOD-1 mutations are both well-established presentations of ALS and these studies may indicate how pathologies of ALS could initiate this novel theory. Both mutations have shown to initiate mitochondrial dysfunction, indicating the cause of overactivation. Nevertheless, these results were contradicted by Tan who proved that neither TDP-43 or SOD-1 mutations caused this localisation in a different cell line.[1,3] Hence, other mechanisms of increased dsDNA in the cytoplasm need to be assessed or whether this experimental approach was flawed. cGAS, cGAMP and STING all seem to be upregulated in ALS mutant cells, indicating this pathway is overactivated. Finally, STING and cGAS inhibitors showed promising results in slowing the progression of the disease however treatments were started either pre-clinically or in early onset which cannot be carried through for human use. Further pre-clinical testing would benefit by applying treatment in later stages of disease to analyse whether the same efficacy of these inhibitors is achieved.

The evidence from these papers indicates that cGAS-STING pathway is implicated in driving neuroinflammation and neurodegeneration and also links this pathway with already established protein pathologies of ALS. The use of cGAS and STING inhibitors shows promising therapies to slow the progression of ALS.

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Pharmacogenomics of Topoisomerase I Inhibitor-Based Antibody-Drug Conjugates in Cancer Therapy

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Antibody-Drug Conjugates (ADCs) are increasingly prescribed in cancer therapy due to their targeted cytotoxic delivery. They're comprised of a humanised monoclonal antibody, attached via a stable linker to a potent cytotoxic 'warhead', the antibody is crucial in targeting tumour associated antigens. The aim of this therapy is to reduce systemic side effects caused by cytotoxic drugs which alone are not specific to tumour-associated antigens. Reducing the minimum effective dose (MED) of cytotoxic drug as well as reducing systemic effects could reduce side effects experienced by patients while targeting the tumour in the most specific and potent way. Pharmacogenomics is the study of how DNA affects an individual's response to drugs. DNA can change the number of drug receptors, the rate of drug uptake or metabolism and excretion, therefore changing individual reactions to medication. Trodelvy is an ADC used to treat most commonly, triple-negative breast cancer. The active cytotoxic element of Trodelvy is SN-38, working by inhibiting the nuclear enzyme topoisomerase I, leading to accumulation and misalignment of DNA, therefore cell apoptosis. Trodelvy has been linked to grade ≥3 neutropenia and diarrhoea, similar to the drug that it is derived from, Irinotecan. Adverse events of Irinotecan have been linked to variations in the gene UGT1A1 – a gene essential in drug metabolism of topoisomerase I inhibitors. Individuals with a homozygous genotype have been found to have increased toxicities from Irinotecan and have benefited from dose reductions due to altered drug metabolism, increased build-up of drug in the body and affected PK. This review focuses on whether individuals with homozygous UGT1A1 genotypes experience more frequent severe adverse events and hopes to suggest whether it would be beneficial to introduce genotype testing prior to administration of Trodelvy therefore determining whether dose reductions or other adjustments should be made to reduce patient harm and increase treatment success.

A rapid review was conducted using databases including Medline (via Ovid), EMBASE (via Ovid), TripPro, PubMed, Web of Science and Scopus. The following search terms were used for identifying literature for screening: (Trodelvy OR Sacituzumab govitecan-hziy OR Sacituzumab govitecan OR SN-38 OR Enhertu) AND (UGT1A1 OR glucuronosyltransferase 1A1 OR UDP Glucuronosyltransferase Family 1 Member A1). Duplicates were removed, and the remaining literature was reviewed and eliminated or kept for critical analysis according to the inclusion and exclusion. The following steps included critically analysing the remaining literature using JBI critical appraisal. Following this, seven studies were included, and results synthesised. Extracted information from the studies included cancer type, demographic of patients, genotype testing results, adverse events and grades experienced.

Analysis of the seven studies identified through the search strategies included variations of genotypes in wild type (*1/*1), heterogenous (1*/*28) and homozygous (*28/*28) participants. All patients had the same regimen, following standard treatment guidelines but varying doses. The homozygous genotype, along with being less commonly found was also associated with most treatment related adverse events. Such include all grade neutropenia, experienced more frequently in *1/*28 homozygous genotype individuals (60.9%) than heterozygous or wild-type genotype participants (28.3% and 22.2% respectively), diarrhoea, nausea, and fatigue. Three treatment related deaths occurred, as well as numerous discontinuation due to treatment related effects. Dose reductions were allowed in certain studies – most commonly utilised by patients of homozygous genotypes with serious adverse events. These side effects were often treated in anticipation to prevent occurrence or lesser the severity – antiemetics, antinausea were often pre-infused before the commencing of treatment. However, growth factor support was not allowed prior to treatment beginning, instead was used to shorten the duration and severity of neutropenia.

This review suggests that UGT1A1 genotype profiling prior to administration of Trodelvy could have considerable benefit on patient outcomes with reduced patient harm. Leading to better patient care and potential for better treatment management. Genotype testing is already implemented in the NHS for 5-flyrouracil chemotherapy in the form of the DPYD genetic test, dose adjustments are made for those who are DPD enzyme deficient and therefore more vulnerable to toxic effects due to lack of drug breakdown. As well as this, the SN-38 derivative – Irinotecan, has had consideration of implementation of a genetic test in the NHS which is already widely used in Europe where dose adjustments occur. It is essential more research into this area is conducted, a cost-benefit analysis is required to ensure implementation into the NHS is most appropriate.

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The impact of PINK1 on the immune system

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PTEN-induced putative kinase 1 (PINK1) plays a crucial role in mitochondrial quality control and is primarily associated with the regulation of mitochondrial homeostasis and the maintenance of cellular health. When the mitochondria are damaged, PINK1 is stabilised on its outer membrane where it dimerizes and becomes active. PINK1 then phosphorylates parkin and ubiquitin in order to flag damaged mitochondria for selective recycling, a process called mitophagy[1]. Mutations in the PINK1 gene, which impair the kinase activity of PINK1 and its ability to flag damaged mitochondria, cause an autosomal recessive form of Parkinson's disease in humans[2]. Additionally, the loss of PINK1's ability to flag damaged mitochondria leads to the accumulation of damaged mitochondria, which keep producing reactive oxygen species (ROS), cause pro-apoptotic factors which are molecules that trigger cellular mechanisms leading to programmed cell death such as TNF, and release mitochondrial DNA (mtDNA) into the cytosol. This ultimately, causes apoptosis to the whole cell. As damaged mitochondria is documented to impact the immune system, a role of PINK1 in immune responses is emerging. In this rapid review, the impact of PINK1 on the immune system was studied.

A rapid review methodology was implemented. Databases Ovid Medline® all, Embase classic + Embase, Scopus, and Web of Science were searched with the key terms "PTEN induced putative kinase 1" or "PINK1" and "(immune or immunity or immunology)" and "Parkin*" and "(active* or inhib*)". Additional sources were discovered through snowballing from references cited in relevant literature. The literature was critically appraised using a Critical appraisal of a laboratory experimental-based research paper. The stressors, duration of measurement, specific markers and significance P value data of each paper were taken and analysed.

Twelve studies met the inclusion/exclusion criteria and were advanced for data analysis. Most studies offered high quality research data using different strategies such as PRC, ELISA, ELISPOT, Western blotting and a form of Florescence (immunofluorescence, fluorescent microscopy, est.). In some papers more than one measurement was performed. The general trajectory of the data supported the hypothesis that PINK1 does have an impact on the immune system.

PINK1 has an inversely proportional relationship with various components of the immune system, which is more profound within the nervous system. PINK1 was found to affect the NF-kB activation though Tollip inhibition[3]. Absence of PINK1 can lead to the activation of the STING pathway therefor increasing IFN-β ,IL-6 and IL-12 indicates that the hypothesis that PINK1 may act as first line management to mitochondrial maintenance and immune suppressor but the immune system is used as a contingency when it is overwhelmed or absent. Therefore, looking closer within this pathways upon the immune system might lead to a new way of mitigating inflammation to the nervous system[3,4].

In conclusion, this rapid review confirms a potential relationship between PINK1 and the immune system. Importantly, this relationship needs to be considered for PINK1 modulators that are being developed to treat Parkinson's disease.

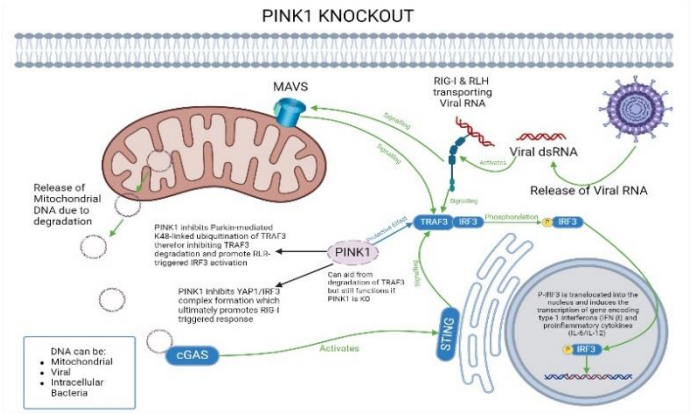

Figure 1 Here a diagram shows the relationship of how MAVS and STING are stimulated and the paths they follow in order to activate inflammatory actions. The green colour on the arrows represent the cumulative increase of inflammation with either signalling, activation and phosphorylation. PINK1 in the diagrams explains how it can interact other than a mitochondrial and MAVS regulator. Diagram created with BioRender[5]

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Penicillin Allergy Delabelling in Primary Care: Healthcare Practitioners' Perceptions and Potential Effects on Patient Outcomes

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Penicillin allergies are the most common recorded drug allergies in the UK, but only a small proportion of those with this label have a true allergy[1]. Penicillins are usually first line treatments for infections as they are known to be safe and effective, but patients with penicillin allergy labels often receive other classes of antibiotics instead. These alternatives tend to have a greater risk of side effects, antimicrobial resistance, and opportunistic infections[2]. Many of these patients will retain a penicillin allergy label for life, never having been tested or had their allergy label challenged[3]. There have been several studies into penicillin allergy delabelling in secondary care but much less research has been done in primary care settings. Understanding primary care practitioners' views on penicillin allergy delabelling is valuable as these healthcare professionals encounter many patients every day, so could play a significant role in delabelling efforts. This study aims to explore primary care practitioners' perceptions on penicillin allergy delabelling, as well as provide suggestions as to how penicillin allergy delabelling could be increased in primary care and improv patient outcomes.

A survey comprising open and multiple-choice questions about perceptions and past experiences of penicillin allergy delabelling was sent to all GP practices across Hywel Dda and Betsi Cadwaladr Health Boards in Wales. Conceptual content analysis was then carried out, coding responses based on different concepts, which were then grouped into themes for analysis.

Results revealed that practitioners working in GP surgeries are generally aware of the risks involved with having a penicillin allergy label but face several barriers that prevent them from removing these labels when appropriate. These include a lack of knowledge and confidence, fear of the consequences of making a mistake and patient refusal. The respondents identified a need for education for both patients and professionals on safe delabelling of penicillin allergies to tackle these barriers. Another significant barrier identified was the poor documentation of penicillin allergies, and the lack of communication about patients' allergies between secondary and primary care providers. A lack of time and money was commonly mentioned by the respondents, with many practitioners concerned about the increased workload that would come with penicillin

allergy delabelling. The main suggestions of how to overcome this involved providing dedicated delabelling services, such as one run by pharmacists.

In order to increase penicillin allergy delabelling in primary care, education for healthcare professionals and patients is required, as well as additional funding to ensure a delabelling programme is feasible. Documentation of allergies needs to be clearer and more detailed, as per guidelines[4], ensuring practitioners have sufficient information to make a clinical decision regarding an allergy label removal. Additionally, hospital staff should ensure any changes to a patient's penicillin allergy label is clearly conveyed in discharge letters, so this can be updated in the patient's primary care records. Future studies should evaluate how successful of these actions are in increasing penicillin allergy delabelling. If these actions are found to be successful, fewer patients should be exposed to the harms associated with non-penicillin antibiotics, and therefore overall patient outcomes may improve.

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Polylactic acid. Is it Stable? An investigation into the stability of 3D printed polylactic acid inserts

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Polylactic acid (PLA)is a biodegradable[1] plastic often used in food packaging. More recently, researchers have been using PLA as a building block to 3D print unique structures including perfusion cassettes.[2] Perfusion cassettes create 3D modules of vascularized skin cells. Perfusion cassettes are 3D printed in mineral oil. Aqueous skin cells added mineral oil is removed. Media is perfused through, to allow the skin cells to grow. This Study aims to investigate the stability of Polylactic Acid when exposed to culture media and mineral oils used for the growth of cells in the perfusion cassette.

Over 4 weeks, a PLA insert design was created and optimized using Open SCAD. 12 inserts were printed using Polylactic acid filament and 3D printed on Ultimaker. All 12 inserts were labelled and weighed. Photos were taken of all the inserts at 2 x zoom and 5 x zoom. The inserts were separated and placed into two different 6 well plates. Inserts 1-3 and 7-9 were given 2ml of culture media[3]. The remaining inserts were given 2mls of Fishers mineral oil. Once all inserts had been filled, the lid was added and the inserts were placed in an oven with a temperature of 37 degrees C. Inserts 1-6 were placed for 48 hours. 7-12 for 24 hours. Once their respected times was up, the inserts were removed, contents removed and placed in the same oven for 30 mins with the lid off. Weights were taken as well as pictures.

All the inserts gained weight showing that the mineral oil and culture remained in the insert after drying irrespective of time exposed. Figure 1 A shows insert number 6 before and after being exposed to mineral oil at. The colour difference is because the brightness of the light microscope was different. Figure 1 B shows how after exposure to mineral oils, oil droplets filled the insert in an irregular pattern. With the culture media, photos taken didn't show clear changes in structure of the PLA implying the culture media has seeped through because they all gained weight. In figure 1 the grid structure remained showing that the structure remained strong after exposure. Observations to mention: Not all the inserts printed the same. Small cracks were seen in the grid structure on 5 inserts. Cloudy discoloration occurred at the base of 3 inserts after exposure.

These results show that based on the 12 inserts, polylactic acid keeps its structural stability however mineral oil and culture media[3] remains on or in the insert and the long-term effects of this have not been investigated. PLA can be unreliable in the printing process due to how the initial weights of the inserts varied and observable cracks found in some of the inserts. The cloudy discoloration observed needs to be studied more to establish weather Polylactic acid degradation has occurred after exposure. Overall, the experiment was effective in showing how PLA remained structurally stable after exposure but due to the small sample sizes and questions raised above more experiments needed to confidently state how stable PLA is when exposed to culture media and Mineral Oils.

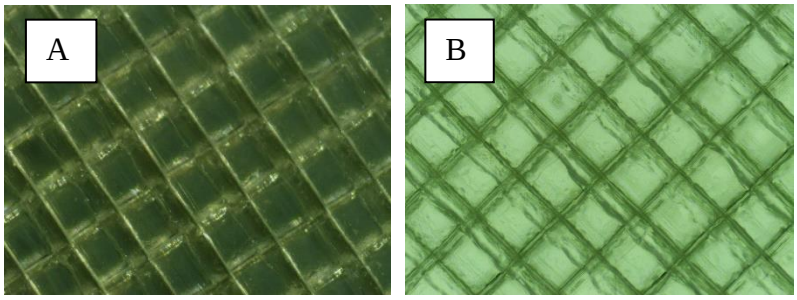

Figure 1

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Determining clinicians' understanding of the choice and dose of antibiotics in adult sepsis patients with acute kidney injury within the Cwm Taf Morgannwg University Health Board – A qualitative study

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Sepsis is a life-threatening condition where the body's disproportionate response to infection causes organ dysfunction. Acute kidney injury (AKI) occurs in up to 50% of sepsis cases[1] and increases the rate of mortality. It is therefore essential that sepsis with AKI is well-managed with evidence-based approaches to treatment. Recent research into the pharmacokinetics and pharmacodynamics of antibiotics in sepsis with AKI has found evidence that antibiotics, when using reduced doses as suggested for renal impairment, have been failing to reach effective levels and higher doses have now been recommended for some antibiotics[2]. However, many existing resources have not yet updated their guidance, leading to conflicting information being presented to clinicians. This study therefore aims to ascertain current practice within the Cwm Taf Morgannwg University Health Board (CTMUHB) hospitals in order to form a basis on which new guidance or training on the use of antibiotics for sepsis patients with AKI can be proposed, if needed.

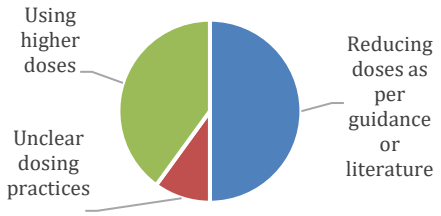
Following ethical approval, a series of semi-structured interviews were conducted with clinicians over a 6-week period in order to explore the prescribing practices of antibiotics for sepsis patients with AKI within the CTMUHB hospitals. Participants were selected using a mix of purposive and volunteer sampling. With consent, the interviews were recorded and transcribed verbatim before being thematically coded and analysed, with a deductive focus on the choice and dose of antibiotics in sepsis patients with AKI, and the rationale behind this decision.

Ten clinicians were interviewed: a mix of consultants, pharmacists and a registrar, whose specialist areas included acute medicine, microbiology, and care of the elderly. All but one participant reported that they saw sepsis patients with AKI daily or commonly. It was reported that primarily junior doctors were the clinicians making a decision on the choice and dose of antibiotics, which was then reviewed by consultants and/or pharmacists. Information on the use of second-line antibiotics was mixed; of the 6 participants who discussed the topic, 3 participants stated they may use second-line antibiotics, whilst the remaining 3 said that they usually would not. Reasons for using second-line antibiotics included AKI severity and bacterial sensitivity to antibiotics. The dosing of antibiotics was a similarly contentious topic, as displayed in Figure A1; of those who reduced dose in line with guidance, 4 used the renal impairment dose reductions stated in local guidelines, and 1 used dose reductions as per the Renal Drug Handbook. Those who stated that they would use the higher antibiotic doses referenced the transient nature of AKI and the importance of treating the infection. Common resources used to aid decision-making included local

antimicrobial guidelines and the Renal Drug Handbook, as well as the pharmacy and microbiology departments.

In conclusion, it is likely that second-line antibiotics and reduced doses are sometimes being used for sepsis patients with AKI within the CTMUHB hospitals; a result in line with a similar study conducted by Mahmood and Hughes3. This may lead to negative clinical outcomes such as longer hospital stays, higher costs, and antimicrobial resistance. However, due to the small sample size, further investigation into prescribing practices is warranted, with a focus on junior doctors, in order to fully ascertain what would be most helpful to be put into place regarding further guidance and training.

Figure A1: Clinicians' responses regarding antibiotic renal impairment dose reductions for sepsis patients with AKI



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Cross-Resistance to Beta-Lactam Antibiotics Following Pre-Exposure to Antibiotics Within Topical OTC Sore Throat Treatments: An Experimental Study

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Antimicrobial resistance is one of the most serious global public health threats currently facing healthcare systems. In a 2023 report, the World Health Organization (WHO) described excessive and inappropriate use of antimicrobials as one of the main factors driving antimicrobial resistance[1]. Despite this, in many European countries there are antibiotic products available for purchase over the counter (OTC) without the need for a prescription. One indication for which antibiotics are available OTC is for the symptomatic relief of sore throat, despite the fact that 85-95% of adult sore throat cases are viral in aetiology and the majority of cases are self-limiting in nature, negating the need for antibiotic treatment. A systematic review conducted by Essack et al. reviewed the antibiotics contained within OTC sore throat products available in Europe; of interest for this project are gramicidin, bacitracin and tyrothricin[2]. In a 2020 paper, Wesgate et al. demonstrated the potential of OTC antibiotic pre-exposure to drive the development of cross-resistance to clinically used antibiotics, including those of the beta-lactam (β-lactam) class[3]. Beta-lactam resistance in Gram-negative bacteria primarily arises due to the production of hydrolytic beta-lactamase enzymes. The beta-lactamase enzymes are classified using the Ambler classification system – an enzyme of particular focus for this project is AmpC, a member of the Ambler class C enzymes, which is becoming an increasing problem worldwide in the context of antimicrobial resistance development.

This project aims to test the hypothesis that the development of cross-resistance following pre-exposure to antibiotics contained within OTC sore throat products (mainly gramicidin, tyrothricin and bacitracin) is due partly to the induction of beta-lactamase enzymes, more particularly AmpC. Five beta-lactam antibiotics were assessed in this project: aztreonam, cefotaxime, cefoxitin, cefepime and imipenem. Clinical antimicrobial susceptibility of Escherichia coli, Klebsiella pneumoniae and Enterobacter cloacae to these beta-lactam antibiotics was assessed before and after OTC pre-exposure through the use of two standard methods: EUCAST disk diffusion and minimum inhibitory concentration (MIC) determination following ISO 20776-1 (2020). Results were compared to the clinical breakpoints outlined by EUCAST. A novel beta-lactamase

activity assay utilising a nitrocefin colorimetric indicator was used to phenotypically assess beta-lactamase activity before and after OTC pre-exposure, to evaluate whether beta-lactamase upregulation was the underlying mechanism behind any resistance development. The bacteria were treated with a beta-lactamase inhibitor, either clavulanic acid or cloxacillin, and any changes in enzyme activity were compared to a control where no inhibitor was present.

The clinical susceptibility testing data collected for both E. coli and K. pneumoniae showed little significant change when comparing the results before and after OTC antibiotic pre-exposure, indicating a lack of resistance development. However, the data collected for E. cloacae highlighted the development of significant clinical cross-resistance to the majority of the tested beta-lactam antibiotics as a result of OTC antibiotic pre-exposure. Combining this data with an evaluation of the beta-lactamase activity assay data allows confirmation of the hypothesis that beta-lactamase enzymes are a driving factor behind the observed clinical resistance. An increase in beta-lactamase enzyme activity was observed following pre-exposure to all three OTC antibiotics when compared to the non-exposed control. Furthermore, the use of different beta-lactamase inhibitors allowed identification of the class of enzymes present within the resistant E. cloacae bacteria. The significant decrease in beta-lactamase enzyme activity levels recorded when E. cloacae was in the presence of a cloxacillin inhibitor (compared to the levels observed with clavulanic acid or no inhibitor present) indicates the presence of ambler Class C beta-lactamase enzymes; class C enzymes are inhibited by cloxacillin but not clavulanic acid[4]. This, combined with the knowledge that E. cloacae is a known AmpC producer, phenotypically indicates that AmpC was induced following pre-exposure to the OTC antibiotics tested, and that this enzyme plays a role in the development of cross-resistance to beta-lactam antibiotics.

The findings of this project demonstrate the considerable risks of OTC availability of antibiotics to treat sore throat, and their potential to drive cross-resistance to clinically used beta-lactam antibiotics, underscoring the danger associated with inappropriate antibiotic use. These results lend considerable weight to the argument against over-the-counter antibiotic availability, echoing the current WHO directives promoting enhanced antimicrobial stewardship and the exploration of non-antibiotic treatment options.

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Exploring the financial and operational impact of prescribing ESA medication on WP10HP prescriptions for people with kidney disease across South West Wales with special focus on the impact on hospital healthcare providers

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Anaemia is a common complication of chronic kidney disease (CKD). It is associated with further complications that can reduce quality of life and increase the risk of morbidity and mortality respectively. This prevalence is due to a reduction in the levels of endogenous erythropoietin (EPO). Erythropoiesis is the process of forming new red blood cells and EPO is central to this mechanism. EPO is released by the kidneys in response to low oxygen levels within the blood[1]. It is a glycoprotein that binds to receptors of cells in the bone marrow, allowing red cell survival, proliferation and differentiation, however low levels result in reduced iron absorption, inflammation and a lowered red cell lifespan. As kidney damage progresses and eGFR decreases, EPO levels also worsen[2]. Lower EPO levels mean lower levels of circulating red blood cells, and therefore lower iron levels, ultimately leading to the anaemia seen in CKD. Currently in Wales, Erythropoiesis-Stimulating Agents (ESAs) are first line for treating anaemia in CKD patients. At this time, they are provided on hospital prescriptions using contract prices, but there is evidence that there may be a better way of providing the injections that could be more cost effective. Recently, there has been a move to provide ESAs on WP10 forms as they are VAT exempt (a cost saving of 20%). This change could result in a large overall cost saving for the NHS, which is a main priority in order for the service to continue to invest in new and advancing medicines[3]. The population in the UK is aging, and as a result it is known that the burden on the health care service is set

to increase. Reducing costs is therefore more important than ever before. The project aims to assess whether changing to provide ESAs on a WP10 prescription dispensed at a community pharmacy would result in a cost saving for the NHS and provide a beneficial improvement to patient care and outcomes.

This project adopted both a qualitative and quantitative approach. A focus group was conducted involving members of the Morriston Hospital Renal Pharmacy Team and themes were isolated from the discussion using thematic analysis. All identifiable data was removed from the transcript and deidentified during the coding process. Five themes for discussion were identified. All ethical aspects were assessed by Cardiff University who granted approval for the project (reference number 2324-09). Data analysis was also conducted based on information about the 356 renal patients that attend Morriston Hospital for their care. This analysis included calculation of the reduction in travel when switching to collection from community pharmacy and the resulting impact on carbon footprint.

Results of the focus group found that members of the hospital renal team did not support implementing the change to WP10HP forms for all patients. They were reluctant to fully trust that pharmacies would be used safely by patients without risk of delay to collecting medicines. Barriers to fully supporting the change were identified in key areas: storage concerns within the community pharmacy, loss of patient contact and increased workload for staff. However, key patients groups that may benefit from the change were also identified, especially with focus on those living in rural areas that are unable to access hospital facilities with ease. This is supported by the data, that showed that changing to WP10HP forms would help to reduce travel and carbon footprint for patients living in identified locations. The following five themes were derived from the focus group: Community limitations, Ownership and autonomy, Change to work patterns, Patient convenience and Travel and practicality.

The proposed change in prescribing format has both advantages and disadvantages, but at this time would not be suitable to implement for all patients. However, there is clear evidence that for some it would greatly improve quality of care and provide a cost saving for the NHS, as well as providing an environmental benefit by reducing travel. It should be offered to patients as an option, especially from an economic standpoint, as cost analysis revealed a VAT saving of 20% would be awarded. However, it is important that patient wellbeing and safety remains paramount, and for this reason, there are certain patients this change would not be suitable for, such as those using homecare at present.

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Is CD81 a Viable Therapeutic Target for Cancer Treatment? A Rapid Review

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Cancer drug development has evolved to focus on generating targeted therapies aimed to deliver precision medicines with less undesirable effects. Preclinical research begins by deciphering underpinning molecular mechanisms of disease progression, by studying the disease in vitro and in vivo animal models for conceptualization. The Tetraspanins are a superfamily of proteins generating interest as potential drug targets in oncology, several of which are undergoing investigations due to their implicated role in organisation of cell signalling interactions and thus processes they may control that contribute to cancer progression, such as metastasis[1]. Cluster of Differentiation 81 (CD81), a tetraspanin protein, exhibits differential expression levels in various cancers, which has led to conflicting reports on the role of CD81 in cancer progression[2]. This resulted in apprehension when considering the therapeutic value of targeting CD81 in cancer therapy, as CD81 has been reported as both a cancer suppressor and oncogene [2]. In this review, comparisons were made between studies investigating expression of CD81 in various cancers and the effects that manipulation of CD81 expression levels had on cancer progression, to discover trends in the data reported between research articles.

Literature databases Medline, Embase, Web of Science and Scopus were searched, utilizing a systematic rapid review approach. A complex, four stage, search strategy was required to retrieve relevant studies. Search one detailed 14 cancer terms separated by 'OR'. Search two included 5 variations of 'CD81' separated by 'OR'. Search three, not used in MEDLINE to avoid accidental exclusion of key articles, was combined with search one via 'adj20', to include research with 'therap* OR treat* OR target*'. Search two and one/three were

combined by 'AND'. Difficulties encountered with searches retrieving articles unrelated to cancer or CD81 led to the addition of search four using 'AND NOT', to exclude articles with any of 14 different terms in the title, separated by 'OR'. Studies were critically appraised using a modified CASP framework for experimental studies. Articles investigating differential CD81 expression in cancer via use of monoclonal antibodies or genetic knock in/knock out of the gene were included in the review.

Twenty-nine articles were retrieved for reading and analysis to determine applicability to the study. Fifteen articles fitting the inclusion/exclusion criteria were eligible for evaluation. Included publications were preclinical studies researching CD81 with respect to a type of oncology, carried out either alone, or in combination with, cancer cell line cultures, patient cancer tissue samples, rodential animal models expressing human or equivalent species-specific cancer, or survival analysis of cancer patient follow up. Methodologies employed by studies were compared to assess quality of procedures and identify bias. Relevant results of studies were extracted to present qualitative comparable findings of CD81's involvement in cancer. Alternative protein levels affected by CD81 expression manipulation aided prediction of possible signalling pathways that may be involved in CD81's involvement with cancer progressive features.

The majority of research in this review demonstrates clear involvement of CD81 in cancer progressive features and regulation of these characteristics, and therefore supports CD81 as a therapeutic target. However, details of subsequent cellular interactions after CD81 expression manipulation are not always extensively explored, consequently undermining CD81 as directly responsible for observed changes in cancer progression. To rectify this, some included studies used other proteins known to be involved in cancer progression as controls alongside CD81. Furthermore, epigenetic gene-silencing due to hypermethylation of CD81's promoter region was hypothesised as accountable for CD81 suppressive activity in some cancers. There is also evidence to suggest that CD81 expression levels and function in cancer cells may be determined by tissue of derivation. Primarily endodermic-derived cancers, indicate CD81 as a cancer suppressor, although CD81 is more commonly seen as an oncogene particularly in cancers originating from mesodermal or ectodermal tissue. Overall, the literature suggests CD81 function in cancer may be determined by cancer tissue origin could account for CD81's differential expression across the board[3].

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An Evaluation of the WNK-OSR1 Signalling Pathway as a Target for Cancer Therapy

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The With No Lysine [K] (WNK) kinase regulates the function of cation-chloride co-transporters (CCC), and therefore it affects ion homeostasis in cells, ultimately governing cell behaviours[1]. WNK kinases stimulate the activity of two downstream kinases, oxidative stress-responsive kinase 1 (OSR1) and SPS1-related proline/alanine-rich kinase (SPAK), via phosphorylation. This, in turn, activates SPAK and OSR1 to go forth and phosphorylate a wide range of ion co-transporters. Due to the reach of the downstream kinases involved in this signalling pathway, an influence over multiple cancer-associated signalling networks, such as TGF-β, Smad2/3 and NF-kB, has been noticed. This has given rise to multiple research studies evaluating the WNK-OSR1 signalling pathway as a potential target for the treatment of cancer progression. Investigations have been undertaken to explore the effects of interfering with these signalling networks, through the WNK-OSR1 pathway, in hopes to observe a therapeutic effect on cancer progression[2]. However, the complexity of the relationship between the signalling pathway and the co-transporters it influences, as well as the differing levels of authority that each subset of WNK and downstream kinase has on them, makes predicting outcomes of intervention difficult.

A rapid review approach was taken on, and a search was developed using the databases Medline (Ovid) and Embase (Ovid). The databases were searched for papers including the terms "WNK" OR "SPAK" OR "OSR1" AND "Cancer". From these gathered papers, articles were screened for their eligibility based on the contents of their titles and abstracts. A PRISMA diagram was used to document the exclusion process. A modified CASP framework was developed and used to assess the quality of each research paper, allowing comparisons of data quality between the articles.

Applying the inclusion and exclusion criteria left 12 papers to be taken forward for further analysis. Each paper was examined, and data regarding major hallmarks of cancer progression were lifted and analysed. This included any data concerning cell proliferation, migration, angiogenesis and tumour growth. For example, through collected data regarding proliferation of cancer cells, it was found that downregulation or inhibition of the expression of WNK1, WNK3 and OSR1 resulted in an overall reduction in multiple measures of cancer progression, inferring a correlation between the WNK-OSR1 signalling pathway expression and cancer development. Through the papers both, in vitro and in vivo experimental data was collected, with majority of the animal studies using either mice, rats, or zebrafish as the subjects of their experiments. This allowed for direct comparison between articles in some cases.

In conclusion, evidence suggests that the WNK-OSR1 signalling pathway could be a successful target for cancer therapy due to its influence on multiple characteristics required for the progression of cancer, as shown in multiple studies over a range of different cancers. From the evidence produced via this rapid review, it is shown that altering the expression of WNK1, WNK2, WNK3 and OSR1 can have positive therapeutic effects regarding cell proliferation, migration, angiogenesis, and other more specific measures of cancer progression such as bone cancer pain and overall survival rate. However, the papers gathered in this rapid review failed to discuss in depth the toxicology implications of the manipulation of WNK expression, therefore further research would need to be undertaken in order to fully evaluate the use of the WNK-OSR1 signalling pathway as a target for cancer therapy.

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Evaluating the views of Cardiff University final year MPharm students on their undergraduate experience: A qualitative content analysis of National Student Survey (NSS) free-text comments of 2022 and 2023 graduates

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Student feedback and reflections are an essential component to learning. Students' views need to be taken into consideration to improve overall student satisfaction. Every year the National Student Survey (NSS) is sent out to all final year students across all degrees within the UK (OfS, 2023) asking for their views on the experience of their entire degree, not only that relating to their final year. Students have from January to April of their final year to complete the survey, which consists of 28 closed questions and one open question. The aim of this research project was to identify student comments on their experiences and put forward suggestions for the school to consider when reviewing the MPharm degree working towards improving student satisfaction.

Free-text responses to the open text question, "Looking back on the experience, are there any particularly positive or negative aspects you would like to highlight?" (OfS, 2023). Excel files were provided for Cardiff 2022 and 2023 MPharm graduates for analysis. The free text responses were coded and from these codes, themes and sub themes were deduced iteratively, with the final version confirmed as appropriate by the supervisor. Ethics approval was not required for the anonymous secondary data (Krippendorff, 2019).

In 2022, 119 students were in the final year. Of these, 85 answered the closed questions and 39 answered the open free text question. In 2023, 106 students were in final year and 78 answered the closed questions of the NSS and 33 answered the open free text question. Students could provide comments relating to more than one theme for positive and/or negative comments and so the number of comments does not equal the number of students. Figure 1 shows the number of positive and negative comments for each of the five themes for 2022 and for 2023. The themes identified from the free-text responses (n=153) were as follows Placements – 33, Timetable – 15, Assessments –15, Teaching and Learning – 72 and 18 in the theme Other.

This study was successful in identifying student views on their MPharm experience via NSS free-text comments and from the analysis, suggestions to Cardiff School of Pharmacy and Pharmaceutical Sciences for consideration in enhancing the MPharm student experience have been identified. This study has limitations in terms of the small number of responses and lack of context to some comments, some focused only on their final year instead of their whole MPharm experience. These could be address through further research for example via interviews or focus groups, and in each of the four years of study.

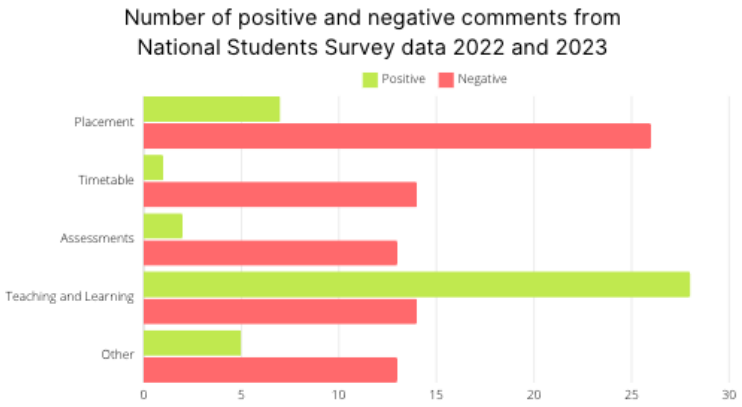

Figure 1: The number of positive and negative comments within each theme using National Students Survey data from 2022 and 2023

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Stability Studies on Hydrocortisone for a Potential Auto-Injector Development

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Hydrocortisone, a corticosteroid, is utilised for treating chronic adrenal insufficiency (more commonly referred to as Addison's Disease), a condition characterized by the insufficient production of essential hormones by the adrenal gland[1]. Of particular note is hydrocortisone's application during adrenal crisis, a life-threatening condition that requires immediate medical attention and intervention. The current standard of care necessitates patients to manually administer their injections using a hydrocortisone emergency kit[2]. However, this method poses significant challenges, as self-administration can be complex and potentially unsafe. Consequently, there is an increasing demand for a hydrocortisone auto-injector; a safer, user-friendly alternative[3]. Despite this demand, the development of such a device is hindered by the limited stability studies on hydrocortisone in a syringe. This study seeks to address this gap in knowledge by examining the stability of hydrocortisone in a pre-filled syringe.

In the methods employed for this study, samples of two potential hydrocortisone molecules, namely hydrocortisone sodium phosphate(HSP) and hydrocortisone sodium succinate(HSS), were prepared in polypropylene syringes and stored for a period of 14 days in a refrigerator. A validated High-Performance-Liquid-Chromatography (HPLC) stability indicating assay was utilised to analyse the degradation of the hydrocortisone molecules over the course of the study. Additionally, physical tests, including turbidity, pH, and visual inspection, were conducted to further assess the stability of the molecules. At day 7 and 14, duplicate samples were removed from refrigerated storage and analysed. Duplicate samples were then subjected to two different temperatures, specifically 25°C and 30°C, for a duration of 24 hours. These temperatures represent real-world conditions that a potential pre-filled auto-injector would be subjected to. 25°C being representative of room temperature storage(RT), and 30°C representing the storage of such an auto-injector in the pocket of a patient.

Chemical stability results showed that Hydrocortisone Sodium Phosphate (HSP) and Hydrocortisone Sodium Succinate (HSS) remained stable within the acceptable range of 90-110% of hydrocortisone remaining, throughout the 14 days of refrigerated storage. HSP displayed no pattern of degradation during refrigerated storage. Conversely, HSS displayed a marginal pattern of degradation, despite staying within range. The physical stability of both molecules was also maintained overall, with no significant changes observed in appearance or pH. The turbidity of HSP decreased linearly across the 14 days, while HSS's turbidity increased initially after day 7, followed by a plateau. Both molecules revealed a significant reduction in turbidity after storage at RT and 30°C for 24 hours on day 7 and day 14. pH values remained largely stable for both molecules throughout the study, even after 24-hour exposure to higher temperature environments.

This study provides preliminary insights into the stability of hydrocortisone when stored in a syringe. Both esters studied displayed satisfactory stability during refrigerated storage for 14 days, and higher temperature storage for 24 hours. However, turbidimetry tests indicated potential instability, necessitating further testing. Notably, HSP displayed potential for being more stable than HSS, no pattern of degradation. These findings, while valuable, are not exhaustive due to factors such as supply shortages and a lack of additional stability and particle count tests. Thus, further in-depth research is required to assess the feasibility of developing an auto-injector device for hydrocortisone, which would greatly improve patient care.

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Pharmacists delivery of, and engagement with green social prescribing. A rapid review of the literature

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Green social prescribing (GSP) is a drug free approach to treat individuals with physical and mental health related conditions.[1] It is based on the premise that spending time in nature engaged in activities which provide physical and mental stimulation has health benefits. cognitive behavioural therapy ()While pharmacists can play a role in signposting patients to nature-based activities there is insufficient evidence to determine that this is happening in practise. The main objectives of this rapid review were to explore pharmacists perception of GSP and to review how and if they are signposting patients to GSP activities.

A search was performed of the Medline via OVID, PubMed and Scopus online databases using keywords and terms mapped from 3 main areas (green social prescribing, barriers/facilitators, and healthcare professionals). An inclusion and exclusion criteria was formed and peer reviewed papers published between January 2017 to December 2023 were subject to screening. A PRISMA[2] flow chart was used to evident the search results. A CASP checklist for qualitative studies[3] was used to critically appraise papers and identify those publication suitable for further analysis. The papers identified by this process were subjected to qualitative analysis.

A total of 12 studies were identified by the review process. Patient, provider, and healthcare professionals' perspectives were captured using a combination of interviews, surveys, focus groups and case studies. Common barriers raised were issues in funding, guidance, confusing ineffective pathways, access and awareness and inconsistencies between localities. Important facilitators were social prescribing link workers, and approaching healthcare in a hollistic, patient centred manner. Some areas of the country were found to be offering more activities than others.[2] Similar themes and challenges were identified included a lack of infrastructure funding, limited access and inadequate knowledge amongst healthcare professionals of the value of GSP schemes. Green social prescribing activities have significant potential in promoting well-being of individuals, addressing health concerns in a hollistic manner, delving into root causes of mental health deterioration. This review highlights the importance of managing barriers and utilising knowledge of facilitators, aiming to get the most out of social prescribing.

This review has identified the barriers and challenges that need to be addressed to enable pharmacists to signpost patients to GSP activities. These include an appreciation of the value of GSP and an awareness of GSP activities available in each locality.

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An Evaluation of Patient and Healthcare Professional Resources to Support Safe Use of Steroids in Patients with Adrenal Insufficiency: A Mixed-Methods Study

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Corticosteroid medications ("steroids") are used to treat a variety of medical conditions. Around 1-3% of the population take steroids, rising to 11% in people aged over 80 years[1,2]. Patients taking steroids for long-term use and/or at high doses are at risk of developing tertiary adrenal insufficiency (AI) from suppression of the hypothalamic-pituitary axis. These individuals should be aware of the sick day rules, which involve increasing their dose of steroids during periods of physiological stress (i.e. intercurrent illness, trauma, or surgery). This helps mimic the physiological response of increased levels of the hormone cortisol under stressful situations. Failure to adjust steroid doses may lead to an adrenal crisis (AC), which can be fatal. The Welsh Endocrine and Diabetes Society (WEDS) have resources for patients and healthcare professionals (HCPs) to improve their understanding of steroid medication and AI, recognising, and preventing AC. The WEDS have developed a steroid 'sick day rule' resource based on the Society for Endocrinology's (SfE's) guidelines. The SfE recommends tertiary AI patients prescribed prednisolone to take their total daily dose in two divided doses ("double and split" dose) during illness. This differs from the British National Formulary (BNF) recommendation which advises all patients with AI to double their normal steroid dose during illness. For example, if a patient with tertiary AI was on a once daily dose of prednisolone, the BNF would recommend the patient to double their once daily dose during illness ("doubled single" dose)[3]. The purpose of this study was to ask HCPs who have seen these resources about their views and perspectives on the usefulness of the WEDS resources and how the resources can be improved. The study also aimed to determine how HCPs currently prescribe steroids to patients with AI during illness, and whether they are prescribed in line with the SfE guidance.

Ethical approval for the study was obtained. The study used a mixed methods approach in three phases: a focus group discussion (FGD), an online survey, and a clinical audit. Members of the WEDS were invited to participate in the FGD or survey depending on availability. Both study designs covered the same topic areas to allow HCPs to provide their feedback on the resources, as well as asking how they would manage two exemplar patients. The FGD was audio-recorded with consent and transcribed verbatim. The qualitative results from the FGD and survey were combined and analysed thematically. The audit was a point-prevalence survey of steroid prescribing in patients with AI during illness. The audit was undertaken over a 6-day period across hospitals in Cardiff and Vale. Quantitative data was collected, and results were analysed using Microsoft Excel.

There were 3 survey responses, 14 FGD participants, and 18 patients in the audit. Seven themes arose from the survey and FGD data. 1) Usability and accessibility of the resources; 2) complexity of the resources; 3) patient and HCP education; 4) simplicity is key; 5) duty of care; 6) thoughts on sick day rule guidance, and 7) necessary improvements. The results produced a diverse range of opinions on the WEDS resources. While some participants found the WEDS resources useful for patients with AI, concerns were raised about their complexity, particularly regarding the 'double and split' dose recommendation for tertiary AI patients prescribed prednisolone. Participants suggested the guidelines need to be more simplistic, providing HCPs with a gold standard to follow, as well as being achievable in an emergency care setting. The audit found that 72% (13/18) of patients with AI were not prescribed steroids according to SfE guidance. Notably, all of these patients had tertiary AI. Common practice involved doubling a patient's regular dose as a 'doubled single' dose during illness.

Although this was a small-scale study, the findings suggest that most HCPs do not adhere to SfE guidance when prescribing steroids. Complexity was a major barrier to use and implementation of the guidelines, directly impacting the prescribing of steroids in practice. This complexity was largely related to the SfE sick day dosing for patients with tertiary AI taking prednisolone. It is essential that the results from this study are used to inform the improvements to the WEDS resources to optimise the safe and effective use of steroids. Future studies should explore patients' views on the WEDS resources and knowledge of sick day rules to help improve the resources.

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Does honey affect malignant cancerous cells, and does it have the potential to be used alone or in combination with other therapeutic drugs to treat colon cancer?

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Honey has been part of the human diet for thousands of years. It can treat many topical conditions, including infected wounds and sore throats, with its many properties. There is considerable interest in exploring the therapeutic potential of honey and its derivatives to treat conditions such as colon cancer. Bowel cancer is the second most common cause of cancer in the UK, with approximately 16,800 deaths every year between 2017 and 2019[1]. Colon cancer is currently treated with chemotherapy (e.g. 5 Fluorouracil) or radiography, depending on the extent and spread of the cancer. Unfortunately, these treatments result in devastating side effects. Thus, we undertook a rapid literature review to determine if honey could be used alone or combined with current therapies to treat colon cancer and reduce side effects.

A rapid review approach was used, and the following databases were searched to identify relevant data: Web of Science, Pubmed, and Scopus. Database searches were performed between 01/10/2023-01/11/2023 using search terms that included colon, liver cancer, chemotherapeutic, honey, and bee-derived products. Snowballing was used to identify additional references. Studies that met the inclusion criteria were analysed critically for quality using the CASP framework. Studies were included if they assessed the effect of honey alone or in combination with licensed therapeutics on colon cancer cells.

Seven publications were critically analysed for their data. The themes identified included cell viability, apoptosis, oxidative stress, and combined therapy results, which were considered for further analysis within papers. All of the papers employed robust methodologies to analyse the impact of honey on colon cancer cells both alone and combined with another therapeutic. Using cell viability and the production of apoptotic makers as endpoints, 50% of the studies examined the impact of oxidative stress and reactive oxygen species (ROS). In contrast, 4 out of 7 papers examined combination therapy.

In some studies, combined therapy shows more cytotoxicity in cancerous HCT-115 and HCT-116 compared to metastatic LOVO cells. The effect of honey alone and combined shows promising effects on colon cancer cells. The impact varies between studies due to the type of honey used and the type of cancer cells it's acting upon. Metastatic LOVO cells resist stress by inducing tumour cell growth, whereas HCT-116/HCT-115 cells undergo apoptosis and cellular death[2]. Treatment with honey increased oxidative stress in cancerous cells with high levels of reactive oxygen species (ROS) and a lowering of antioxidant enzymes. ROS increases pro-apoptotic proteins and degrades anti-apoptotic proteins by catalysis and phosphorylation[3]. There was also an increase in pro-apoptotic markers within cancerous cells, which can lead to cellular apoptosis in HCT-115 or HCT-116 cells, which resulted in low cell viability. The overall effect is programmed cell death in cells through either an intrinsic or extrinsic pathway[4]. Both types of apoptosis lead to the destruction of colon cancer cells by shrinking the cell and nuclear fragmentation, leading to phagocytosis of blebs and membrane destruction[4].

Overall, honey has significant potential for treating colon cancer, with promising findings in vitro indicating an increase in oxidative stress that leads to apoptosis and a decrease in cell viability. Honey also works better when combined with specific colon cancer cells, such as HCT-116. Honey is likely highly acceptable to patients due to its palatability as both a preventative and curative approach. Factors such as delivery method, doses, and compatibility must be considered when testing for patients. There is a need for further research to determine how honey alone or combined will affect patients in vivo, particularly in terms of safety, side effects, and delivery into cells. This research will be insightful for other bowel cancers, preventing the deliberating effects of traditional therapeutics for patients if considered safe in colon cancer therapy.

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The effect of Propylene Glycol as a component of e-cigarettes on the oral microbiome

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E-cigarettes, or vapes, are electronic nicotine delivery devices that were originally intended for use as an aid in smoking cessation. In recent years, their popularity has increased significantly, but ongoing research is exposing the negative impacts that e-cigarettes can have on the user's health. E-cigarettes contain a reservoir of liquid comprising a host of chemicals, including nicotine, propylene glycol (PG) and glycerol, which are heated into vapour then inhaled by the user. Aerosolised PG is well established as a disinfectant and has previously been demonstrated to exert a bactericidal action against various microorganisms. However, the majority of studies of aerosolised glycols were studied pre-1950. When e-cigarette vapour is inhaled, the oral cavity is immediately exposed to a number of chemicals, including aerosolised PG. Within the oral cavity, the microbiome consists of a diverse range of commensal bacteria, which majorly contribute to the defence against opportunistic pathogens. Changes in the composition of the microbiota can lead to weaker protection against invasion of harmful microbes, and therefore puts the host at greater risk of developing oral diseases, such as periodontitis[2]. Given the antimicrobial nature of aerosolised PG, it is important to consider whether its presence in e-cigarettes is harmful to the existing microbiome in the oral cavity. This rapid review compares relevant literature to evaluate whether PG in e-cigarettes causes a detriment to the oral microbiome. It aims to gain a greater understanding of the impact of e-cigarettes and their associated oral health implications.

The study was conducted using a systematic review approach. Research articles were gathered using multiple databases: Web of Science, Medline via Ovid and Scopus. Search terms used were 'Propylene glycol' or 'glycol' and 'e-cig*' or 'vap*' and 'microbiome' or 'microbiota'. In Medline via Ovid, the MeSH subheadings "Electronic Nicotine Delivery Systems" and "Microbiota" were inputted. Articles were also found through snowballing from relevant reference lists. The articles were then screened and assessed for relevance using the inclusion/exclusion criteria. The selected articles were critically assessed using critical appraisal checklists and conclusions were drawn by considering their results and their quality level.

After implementing the search strategy, twenty research articles were included in the rapid review. Out of these, thirteen were human studies and seven were laboratory studies. The data collected in the human studies proved to be more useful with regards to the effect of vaping on the microbiome. Nine of these used DNA sequencing techniques to identify changes in large numbers of species present in the oral cavity, whereas the laboratory studies only tested a small number of species in each study. However, the laboratory studies produced more useful data about how propylene glycol specifically exerts bactericidal action within e-liquids due to their ability to control PG concentrations. The key findings of the study are that there is a significant change in the oral microbiome after it is exposed to e-cigarette vapour, but there is conflicting evidence about whether this is caused by propylene glycol. There is also disagreement between the studies about whether the addition of other components, such as nicotine and flavourings, enhanced or reduced the bactericidal action. Importantly, there was clear evidence that the alterations to the microbiome increase the user's risk of developing periodontitis and oral candidiasis.

Whilst conducting the review, it was clear that most existing research focusses on the effect of e-cigarettes as a whole, rather than the specific effect of PG as an ingredient. The in-vitro studies were the only ones to state and/or change the concentration of PG in the e-liquids, and they found varying results about its bactericidal action. Whilst propylene glycol has a proven bactericidal effect in aerosolised form, there is currently opposing data regarding whether changes in the microbiome are attributable to PG within the e-vapour. Therefore, it would be beneficial to conduct further human studies, in which participants use e-cigarettes with varying concentrations of components, including PG, nicotine and flavourings. Their microbiomes could then be compared to each other and non-users, which would produce data to draw strong conclusions about whether it is PG, another ingredient, or a combination of these that is causing the bactericidal effect.

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Care home staff perspectives of a pilot switch from oral nutritional supplements to a homemade milkshake alternative treatment for malnutrition

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The mainstay approach for treating malnutrition involves prescribing oral nutritional supplements (ONS)[1]. While little data exists, supplements are anecdotally unpalatable for patients and correlate with poor patient outcomes and economic losses[2]. This provides an incentive for a switch from ONS to a fortified food approach where ingredients are added to existing food/drinks to maximise micronutrient intake[3]. The homemade milkshake recipe (HMS) was produced by Hywel Dda University Health Board Dietitians using guidelines for food fortification[3]. The homemade milkshake (HMS) mimics the contents of ONS to provide the same nutritional value with the aim of improved clinical outcomes and reduced cost implications. Spending on ONS was £187million in England and Wales annually as of 2020[4] with one review showing an average of 78% compliance equating to a £41million cost of waste[2]. Care homes provided a suitable pilot population due to the existence of long-term monitoring and a high volume of ONS prescribing.

Senior staff from five care homes who were part of the HDUHB milkshake pilot project were recruited to participate in a semi-structured interview to explore their experiences and perspectives to date. A waste audit was completed in a further three homes for evaluation of the economic impact of the switch from ONS to the HMS. Thematic analysis of the interviews lead to the formulation of several overarching themes, and subthemes representing the views of the interviewees.

A strong consensus opinion in favour of the milkshake was reported at all sites. Staff response was divided into four overarching themes: (i) Resident perception, (ii) Resident health impact, (iii) Impact on staff routines, and (iv) Economics of waste and cost. Staff linked improved palatability and acceptability of the HMS to compliance as many residents are unable to verbally communicate due to their cognitive status. Another subtheme of resident perceptions was the suitability and individuality of the HMS for residents. Flavour was identified as a key drawback for good compliance of the HMS. Improved compliance correlated with a reduction in waste estimated by staff in interviews: an average of 40% of ONS to 2% of the HMS. The waste audit correlated with this but to a lesser extent. For forty-two residents, a cost-saving of £32,028 was found from 22% non-compliance to ONS. Positive health benefits, mainly weight gain, were reported as observed in residents where the twice-daily HMS regime was followed. A key trend raised that resident weight is multifactorial due to the degenerative and cognitive decline seen in the residents. These homes reported a reduction in dietetic referrals made. Four out of five homes noted no extra pressure on staff workload as milkshakes had been distributed previously. Two outliers explained that preparing the HMS initially introduced strain on the kitchen, but they have since been able to adapt and denote that the HMS is more practical. The HMS was reported as easily adaptable, versatile, made-to-demand and easy for all staff to prepare. While 4/5 homes deemed the HMS as cost-effective, it was implied they wouldn't continue if costs weren't reduced as the transition of cost from the NHS to the care home caused concern.

This study indicates a successful roll-out of the HMS pilot. While perceived clinical outcomes are proving the milkshake to be effective due to a 38% improvement in compliance from interviews, recommendations mainly surround cost. ONS is funded by the NHS, however, the milkshake does not fall under a formulary so is currently funded by the home. This is a key issue for many of the pilot homes. The savings from wastage of ONS (£32,028 for three homes), reduced dietic referrals and potentially reduced cost of malnutrition-associated complications could allow for NHS-funded milkshakes. Further studies on the exact cost of these measures could support this. While the HMS was considered versatile, interviews revealed more flavours similar to those available as ONS would further improve compliance as aligned with Hubbard et al where an 18% increase in compliance to ONS was found when varied flavours were used (2). Cost-savings could allow for the redistribution of funds into more forms and flavours of fortified foods and a larger focus on screening and assessment of malnutrition. Expansion of the project would first require a wider demographic pilot population and consideration of the effect of confounding factors, such as the influence of multiple disease states on clinical outcomes. Additional quantitative analysis of resident health is required to challenge the findings of this qualitative study.

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The Stability of Catecholamines in Intravenous Preparations for Neonates: A Rapid Review of the Literature

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The inotropes epinephrine, norepinephrine, dopamine and dobutamine are all catecholamines which are used to treat hypotensive cardiac events in neonates to prevent premature death[1]. Drugs are administered intravenously through syringe drivers or infusions at precise concentrations and are weight dependent. This requires the majority of solutions to be made at ward level[2]. Reconstitution at ward level brings about risks of contamination, dosing inaccuracy and errors in preparation, all of which could contribute to neonatal fatality from medicine mismanagement. Subsequently, The Neonatal and Paediatric Pharmacy Group (NPPG) framework[3] aims to direct neonatal intravenous administration towards the standardisation of these high-risk drugs. At standardised concentrations, 'ready-to-administer' injectables have the potential to be a safer method of drug preparation, but also promote mass manufacturing which is both cost effective and efficient. The stability of pre-filled injectables containing the catecholamines needs to be further investigated due to the limited research on the long-term stability of the drugs and how concentration degradation affects shelf life. Concentration degradation occurs commonly through heat degradation, photodegradation, oxidation and pH[1]. This rapid review investigates the current physio-chemical stability evidence of the forementioned drugs with the objective to guide future stability studies to potentially extend catecholamine shelf life.

A rapid review methodology was adopted; the databases Medline, Scopus and Embase were searched for relevant literature. The search included the four drug names combined into themes using "AND". The fundamental theme was "drug stability OR shelf life OR drug storage OR drug formulation". Additionally, synonyms to the "injectable route of administration" were combined with "AND". For all themes, synonyms and conjugations were included, producing an extensive initial search. The search scope was narrowed to English language articles and relevant titles were gathered, and duplicates were removed. Abstracts were then screened, producing 139 papers. The papers that did not meet the defined inclusion criteria for the rapid review were removed. 38 of the 139 papers were deemed suitable for further analysis, of which seven papers were taken forward for quantitative and qualitative analysis.

Of the seven papers, two papers looked at epinephrine, three papers at norepinephrine, one paper at dobutamine and one at dopamine. All studies explored thermal degradation as a primary variable for stability. The papers all adopted a validated High Performance Liquid Chromatography (HPLC) stability indicating assay and four papers used ultraviolet light as the detection technology. All papers agreed optimal storage conditions to be refrigerated or frozen temperatures to maintain above 95% of the initial drug concentration. Epinephrine showed stability for 6 months at 2-8°C, norepinephrine showed potential stability for 1 year at both -20°C and 5°C. Dopamine remained stable for 6 months at -20°C and for 3 months at 4°C and dobutamine showed stability for 42 days when stored at 4°C. Secondary variables of stability were investigated including visual inspection, changes in pH and photodegradation.

Suboptimal sampling techniques and discrepancies with physical observations in some studies meant the HPLC stability indicating assays were not conclusive in determining a reproducible shelf life. Inconsistency in shelf life can be attributable to the variations in study duration, the conditions applied, container type and that sample formulations were not consistent throughout the papers. Furthermore, sample concentrations were wide-ranging with most exceeding neonatal dose recommendations. The NHS Pharmaceutical Quality Assurance Committee outline the standard protocol for deriving and assessment of stability for aseptic preparations[4]. These 'gold standard' recommendations were applied to the existing pharmaceutical research to identify the gaps and deficiencies within the current field[4]. These shortcomings prompt the need for future advancements regarding the pharmaceutical stability of pre-diluted injectable preparations.

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Evaluating 2022 and 2023 Cardiff University final year pharmacy students' perception of their experience by analysing free-text responses to the National Student Survey

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The National Student Survey (NSS) is a questionnaire annually sent to, and to be completed by, final year undergraduates at universities across the United Kingdom (UK)[1] asking for their views on the entire duration of their degree. The NSS anonymised survey first launched in 2005[2] and it comprises a series of closed, and one free-text open question[1]. The free-text question allows for students to provide positive and negative perceptions on their individual experiences, and since the survey first launched, results of the NSS have motivated change for many universities across the UK[2]. This research aims to evaluate views of Cardiff University Pharmacy undergraduates from the 2022 and 2023 NSS cohorts.

Free-text data from the NSS 2022 and 2023 fourth year pharmacy cohorts was obtained via separate excel documents provided by Cardiff University for the analysis. Ethical approval was not required as the study is dealing with secondary anonymous data. Using the steps of qualitative content analysis[3], the positive and negative comments were coded in excel with similar codes then collated and labelled as themes. With further immersion in the data and re-coding on several occasions, the themes were finalised with confidence. The data was presented to the supervisor who confirmed the themes as appropriate for analysis.

From the 119 final year students in 2022 and 106 in 2023 a combined total of 79 students responded to the open and closed questions of the survey (43 from 2022 and 36 from 2023). A further total of 72 students (39 from 2022 and 33 from 2023) completed the free-text question analysed in this study. After coding the data and finalising the themes, five main themes were identified: 1-covid, 2- university arranged placements, 3-teaching, 4- support and 5- community. Theme 1 results showed post-pandemic blended learning (online and in person) has been welcomed by many students along with increased opportunities of face-to-face groupwork as a method of learning post-pandemic, this providing opportunity for good engagement with peers. Students valued university arranged placements however, for 2023 students the pilot year for incorporating the new Health Education and Improvement Wales (HEIW) placements at such short notice did create some challenges with opportunities for further supervisor education suggested to be made. The teaching quality of the pharmacy degree was praised by both years generally with lecturers, external contributors and teacher practitioners being included in the positive comments of teaching quality. An enhancement area identified was for more timely uploading of materials to the virtual learning environment learning central, again via staff education. There was recognition of positive support for students i.e. from personal tutors and from resources and support tools such as the library and Padlet® (discussion board), although opportunities of further improvement were identified regarding student well-being and support for students who have failed an assessment; a further opportunity recognised for the school to enhance.

The study was successful in that a range of positive and negative views of individual students have been analysed and have provided some useful points for the school to consider. Often it was found that helping people other than the students first will consequently allow the students to benefit. A limitation to this study is that the free-text comments provided by students are brief and not all students provided comments. Future work opportunities would be to further interview students of the study to expand on their comments for more specific evaluation and feedback, and at various time-points during the degree. Additionally, recruiting more students to participate would allow a better representation of the year allowing account for different aspirations, experiences, and expectations of the course. Analysis of results has resulted in several suggestions being developed for the school to consider as it continues to develop the MPharm at Cardiff.

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Patients' views and experiences of side-effects and how they are reported

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Adverse drug reactions (ADRs) are an increasing health concern, causing considerable physical, psychological and economic impacts[1,2]. The yellow card scheme (YCS) is the UK ADR spontaneous reporting system, allowing patients and healthcare professionals to report adverse drug reactions[3]. Research has shown that patient reports could provide a beneficial insight into real-world situations and are a key aspect of pharmacovigilance.[2] Despite this, under-reporting by patients remains a significant issue that needs to be addressed.1 The aim of this study is to explore possible reasons for low levels of reporting by patients.

Following ethics approval, members of the South Wales public who had experienced an ADR were invited via social media outlets such as Facebook and WhatsApp to participate in an online focus group on Zoom. Healthcare professionals and those involved in the yellow card champions scheme were excluded from the study. Written informed consent and demographic information via a survey was obtained prior to participation in a focus group. The focus groups were audio and video recorded via zoom and discussions were transcribed verbatim. A thematic analysis was executed to identify fundamental themes.

Four focus groups, involving a total of 11 participants took place. The sample consisted mostly of females between 18-30 years of age. Participants were uncertain around the concept of a "side effect" with varying degrees of understanding on the topic. All participants had suffered side effects that were severe in nature affecting them physically, psychologically and cosmetically. The majority of participants sought help from healthcare professionals such as their General Practitioner (GP) or community pharmacist. Difficulties in obtaining a GP appointment outside of working hours was a key barrier preventing individuals from accessing their GP. None of the participants had any concept of the yellow card scheme (YCS) and side effect reporting. Despite this, participants felt reporting of side effects was vital to ensure the safety of medications on the market and prevention of patient harm. They suggested that awareness of the YCS could be increased via posters, social media, QR codes, online prompts, coffee mornings and letters sent home to parents from schools.

If patients are unsure around the concept of a side effect and don't know about the YCS, reporting rates will continue to fall. This small-scale exploratory study has identified some possible concerns but also some opportunities to engage patients in ADR reporting. However, the sample may not be fully representative of the Welsh population as mostly females from an ethnic minority background participated. Patient education by healthcare professionals on side effects is vital to tackling this issue. While increased promotion of the YCS via social media and advertisements in GP surgeries as well as pharmacies is a crucial aspect of increasing awareness of ADR reporting systems in the UK. Further research must be undertaken to understand the extent of these issues but also to investigate how healthcare professionals can facilitate this process.

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Targeting The Enzyme, PINK1, With Small Molecules As A Novel Strategy To Treat Parkinson's Disease

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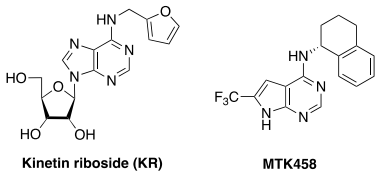
Parkinson's disease (PD) is a condition affecting an estimated 10 million people worldwide[1], but there is no cure available. The fundamental basis of PD treatment is Levodopa, usually given in combination with other medications, which work only to improve the symptoms of PD such as tremor, stiffness and slowness of movement[2]. Unfortunately, treatment with Levodopa possesses many drawbacks including debilitating side

effects and a loss of efficacy with consistent use (2). Therefore, there is a clear demand for a PD therapy that not only ameliorates the symptoms, but also slows down progression of the disease, with the aim of ultimately curing PD patients. Mitochondrial dysfunction is heavily implicated in the pathology of PD, and one of the key enzymes that contributes to this is PTEN-induced kinase 1 (PINK1), whose loss-of-function mutations cause PD in humans[3]. This highlighted the activation of PINK1 as a potential strategy to develop new PD treatments. The first PINK1 activator reported was the nucleobase, kinetin[4], which acts as an adenosine triphosphate (ATP) neo-substrate, since ATP is required for PINK1 to function[4]. To date, only a handful of PINK1 activators have been reported. Here, a rapid review is executed to determine whether small molecule activation of PINK1 represents a viable treatment option for PD.

To address the research question that targeting PINK1 would be a good method of treating PD, a rapid review was undertaken. Three databases, Scopus, Medline (Ovid) and Embase (Ovid), were searched for terms including and related to 'Parkinson's disease' AND ('activ* adj5 PINK1') AND 'therap*' OR 'treat*'. Additional references were found by snowballing from the citations of relevant publications. The research papers were then screened against inclusion and exclusion criteria, with the relevant studies advancing through the rapid review for analysis. The studies were critically appraised using a modified CASP checklist for laboratory experimental-based research papers. To facilitate further investigation, certain details including experimental unit, methodology, measurements taken and proof of PINK1 activation were extracted.

A total of seventeen research papers met the inclusion/exclusion criteria, demonstrating experimental measurement of small molecule activation of PINK1. Of these, nine papers were found to be high quality studies that were particularly pertinent. This included five studies investigating structural variations of the ATP neo-substrate, kinetin, including kinetin riboside (KR) and MTK458 (**Figure 1**). The four other studies explored alternative methods of targeting PINK1 such as depolarisation of the mitochondrial membrane, and increased PINK1 expression. These potential drug molecules were studied in a variety of environments including in different types of cells, neurons and animals. Since the discovery of kinetin[4], the concept of activating PINK1 to treat PD has advanced and while this rapid review found that kinetin itself has no use as a clinical PINK1 activator, its structural analogues, KR and MTK458, both showed very promising results, with MTK458 being found effective in a PD mice model (2). Additionally, a further twelve small molecules were examined, each with a unique mechanism of action, but all fundamentally activating PINK1. Although these molecules showed promise for activating PINK1, particularly niclosamide, there is currently not enough evidence to make any precise conclusions regarding their ability to treat PD.

To summarise, this rapid review finds evidence that PINK1 can be used as a target to treat PD, and suggests multiple small molecules that activate PINK1, providing neuroprotection as a result. Of particular note, KR and MTK458 highlight an exceptionally promising method of activating PINK that could advance to clinical trials. Although other molecules investigated, such as niclosamide, do represent favourable strategies, these will require more research before being considered for progression. The findings of this rapid review could have crucial implications, transforming the way treating PD is viewed towards a disease-modifying approach, which would massively benefit the lives of patients suffering from the disease. The results would also have an immediate implication on research, as this rapid review highlights PINK1 as an effective drug target that could be exploited not only in PD, but also in other neurodegenerative diseases in which PINK1 plays a role, so pharmaceutical companies may choose to fund more comprehensive research.



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A Rapid Review of Long-Term Stability of Solutions Containing Morphine, Midazolam, Rocuronium or Dinoprostone to Aid in the Development of Standardised Solutions for Neonates and Children

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Currently available products being used by the NHS must be discarded within 24 hours after reconstitution, this can lead to incredible product wastage[1]. Personnel time is also extremely important in secondary care, where the inability to prepare these solutions ahead of time results in significant periods of personnel time being wasted[2]. Studies have also suggested that up to half of all intravenous (IV) doses made directly on the wards are associated with errors[3]. By providing IV infusions which are prepared ahead of time at an external manufacturing facility with extended shelf lives, these issues could be resolved. The shift towards standardised IV infusions has shown improvements in safety and efficacy globally, with nursing and pharmaceutical time being reduced by around 60%[4]. However, before this transition takes place, the potential for long-term stability of these solutions must be reviewed and compared to current 'gold standards' of stability testing to determine if they are viable for the process of standardisation[5].

A rapid-review of the literature was conducted on three key scientific databases: 'Embase Classic', 'Medline' and 'Scopus'. This process yielded a total of 14 papers which were critically appraised using an adapted CASP checklist to ensure the validity of the stated results. Insufficient information was found to comment on long-term stability of solutions of rocuronium or dinoprostone. Therefore this review provides a good overview of the long-term stability of solutions of morphine or midazolam. The studies investigated a wide variety of packaging materials including: syringes, vials and infusion bags stored in a variety of environments ranging from freezing to accelerated degradation studies at higher temperatures.

The data collected in this review strongly suggests that solutions of morphine or midazolam demonstrate potential for long-term stability and shelf lives far beyond the currently adopted 24 hours. Evidence is provided to suggest that elevated temperatures can accelerate changes in midazolam concentration in syringes possibly due to solvent evaporation. This phenomenon is not exhibited in studies conducted in polyolefin infusion bags. However, study periods for midazolam in infusion bags did not exceed one month duration. Morphine demonstrated improved stability when stored in polyolefin infusion bags instead of syringes. Multiple studies indicate that storing at room temperature is suitable. In fact, a precipitate that was difficult to dissolve formed in solutions of morphine that were refrigerated, this was linked to higher concentrations of morphine. Morphine solutions that are terminally sterilised in polyolefin infusion bags could be stable for up to 3 years at room temperature[3]. However, it is important to note that the studies included in this review do not meet all of the 'gold standard' requirements for deriving and assessment of stability[5]. More research would need to be done with study designs that adequately meet all of the standard protocols before these solutions could be approved for licensing and use by the NHS. There is also insufficient literature available to comment on long-term stability of solutions of rocuronium and dinoprostone. Thereby, identifying a gap in knowledge that could potentially be exploited for future research.

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Ocular Toxicity of Antibody-Drug Conjugates in Cancer Therapy

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Antibody-drug conjugates (ADCs) are targeted medicines that deliver chemotherapeutic agents to cancer cells. A cytotoxic agent is attached to a monoclonal antibody via a linker which allows it to bind to a specific target expressed on cancer cells. After doing this it is engulfed into the cell where it can then release the cytotoxic drug into the cancer cell. With this in mind, ADCs are extremely useful in the treatment of cancer as they are targeted straight to cancer cells, meaning that healthy cells are left undamaged[3]. This is unlike many other chemotherapy treatments. It is important to patients suffering from the disease of cancer as it limits the side effects associated with chemotherapy and allows a more direct chemotherapeutic treatment to the cancer cells rather than destroying healthy cells in the body. Therefore, this makes it an active and crucial research area as there are currently only thirteen licenced ADCs on the market, and there are many ADCs for different cancer types in clinical trials[4]. One of the fundamental challenges of antibody-drug conjugates currently faced by researchers is surrounding the unfavourable side effects this class of drugs has on the eyes. Findings indicate, it mostly causing issues with the cornea[2]. Furthermore, studies have also shown that side effects can be serious enough for the dose of the drug to be reduced, however mechanisms causing ocular toxicity are not yet fully understood. Crucial work in this area continues in order to comprehend this further. This work will evaluate the experimental literature available reporting on antibody-drug conjugates and the mechanisms that may be involved in causing both on-target and off-target ocular toxicity. This is with an aim to add a greater understanding into this key issue, and to further aid and support research.

The database Medline was used to enter the following search “cornea OR ocular toxicity AND antibody-drug conjugate 0R ADC”. This allowed me a rapid review approach to be taken. Further references were then found and selected from citations of relevant literature. To refine and modify the literature sourced, I used a CASP framework to ensure that only the studies that demonstrated experimental research into the mechanisms of ocular toxicity from ADC’s were selected.

Common ocular side effects associated with antibody-drug conjugates consist of low-grade corneal epithelial changes which are characterised as cystoid lesions, keratitis, blurred vision, conjunctivitis, and dry eye[1]. The incidence of these adverse effects are all associated with the initiation of an antibody-drug conjugate, however, they are reversible and all the side effects from ocular toxicity seem to resolve upon drug cessation[2]. This ocular toxicity can be mediated by multiple mechanisms that can be subclassed into two types. These are ‘off-target’ and ‘on-target’ toxicity. Although both of these sub-classes of toxicity have been shown to have an effect on patients undergoing treatment with antibody-drug conjugates, the mechanisms are yet to be fully understood.

As mentioned, there are currently thirteen antibody-drug conjugates approved for use by the FDA. All of these ADC’s aim to treat different forms of cancer, and all are specific to a different biological target4. This has made understanding antibody-drug conjugate associated with ocular toxicity a challenge for researchers as there is not a clear mechanism linking these drugs and the side effects they cause.

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An investigation into the ‘Heart Failure Service Redesign’ in Swansea Bay Health Board

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Heart failure is a complex multifactorial health problem which is a leading cause of morbidity and mortality in the UK. It is caused by structural abnormalities or impairment in the heart, meaning the cardiac output is not sufficient to keep up with the metabolic needs of the body. It costs the NHS billions to manage heart failure

patients due to the cost of medications and complex hospital admissions. To date there are no nationally implemented guidelines on heart failure, and so heart failure management varies across the country[1]. The 'Heart Failure Service Redesign' in Swansea Bay health board is the first service of its kind in Wales which attempts to identify patients that have heart failure and provide them an annual review. This service is led by the heart failure team in Swansea Bay who aim to see 5000 patients annually, in hope to prevent disease progression and provide specialist management of the condition. This project aims to investigate the new service in Wales and critically analyse its implementation, benefits*, and* limitations*,* but also the opportunities for development.

It was important to become familiar with the identification and management of heart failure before assessing the heart failure service. To this end, reading upon cardiology journals, and current guidelines from NICE, provided the fundamental information needed to delve into the subject of heart failure. The project was helped by visiting the experts within the annual review team which gave this project first-hand information about the service, its aims, benefits, but also the limitations and how they can be addressed. To appreciate the process of identifying patients and allocating appointments, this project was given anonymised patient records to analyse. Using excel spreadsheets, an algorithm was created which analysed patient factors, and depending on a combination of factors, patients were allocated an appointment to the annual review service or a referral to the GP or cardiologist. This system was then compared to the current appointment system used by the heart failure service and identified gaps in the data and how future developments could be made.

After meetings with experts in the annual review service team, it was identified that from the start of the process the health board had perhaps under equipped this new service, and a lack of staff training meant that the process was very slow and inefficient from its introduction. This information could have had some bias, but the data suggests that in the first month of the service, only 43 patients were seen, so the staff reporting such things had a valid basis. Secondly, the data provided by the GPs often proved difficult to utilise due to incomplete data sets, for example, patient would be on the register with no information about if they had an echocardiogram, or if they ever had an appointment with a cardiologist. Consequently, this impacted the appointment system as patient information could not be fully analysed. Furthermore, the algorithm created from excel found that the appointment system used by the healthcare team was inefficient since they were assessing each patient on a case-by-case basis. This was very time consuming. Also, there were inconsistencies in the team's allocation of appointments, where two patients had the same baseline factors, one was given an appointment while another was not. The algorithm created using excel had a 78.1% success rate compared to the appointment system used by the service team. Given the inconsistencies in both appointments systems, the service teams, and the algorithm, it emphasised that further patient parameters need to be considered to create a more accurate appointment system.

Although the health board had provided permanent funding for this new service, a lack of suitably trained staff in fields such as data collection was a problem. This increased the time to collect and interpret data which therefore affected the appointment allocation system. Consequently, it led to patient appointments being delayed. One solution would be to provide staff with training in data analysis to increase the efficiency in data handling and spend more time seeing patients. Secondly, due to GPs being their own external contractors, they have limited time, funds, and staff. This meant that it is not always possible to dedicate time and staff hours to update patient records. This is the main issue that led to poor data availability. This shows the need for primary and secondary care services be involved in sharing of data, and this should be governed by a data quality assurance provided by the health board which ensures the minimum level of data is inputted correctly into GP records. This data would facilitate the heart failure team in analysing patient records from GPs and therefore making it more efficient for the heart failure team to allocate appointments. The algorithm created, highlighted the gaps in data, emphasising the need for more patient parameters such as patient comorbidities. This could increase the accuracy of the algorithm in ensuring the correct patients get allocated an appointment. This service provides specialist care to heart failure patients which they otherwise may not get, and as great a service it is, there are obstacles that need to be addressed to best utilise this service.

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Antibiotic Therapy in Sepsis Associated Acute Kidney Injury: A Qualitative Study of Healthcare Professionals' Views and Experiences

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Sepsis is a serious overreaction to an infection which can lead to organ failure and even death, early diagnosis and treatment is therefore essential for the survival of such patients (1). With poor management, an acute kidney injury (AKI), or sepsis associated AKI (SA-AKI), classified as structural damage to the kidneys, disrupting their regular function may occur, resulting in complications such as dehydration and confusion (2). The administration of antibiotics is an essential step in the successful treatment of SA-AKI, but with impaired renal function, as seen in AKI, complications regarding the use of such drugs could arise. The standard dose of an antibiotic could now cause adverse reactions and further damage to the kidneys, while a dose reduction may not be adequate to treat the underlying infection (2). A lack of specific guidance surrounding SA-AKI, and with most resources focused on dosage recommendations based on chronic kidney disease (CKD), differences in patient management may occur, which could have detrimental effects on patient outcomes. This project therefore aims to gather data on how SA-AKI is managed in hospitals within Cwm Taf Morgannwg University Health Board (CTM UHB), exploring healthcare professionals' views on resources available to support decision making for this patient group with an aim to provide evidence for the improvement of such guidelines or creation of new practice standards.

A semi-structured interview schedule was designed by the research team with input from pharmacy staff based in CTM UHB. Ethical approval was obtained and healthcare professionals with experience in the antibiotic management of SA-AKI were invited to interview. Those willing to participate underwent a recorded interview, with questions focusing on their views and experiences in managing SA-AKI. A total of 10 interviews took place and data from each was transcribed by the researchers and later checked for any accuracy errors. A qualitative approach was adopted to assess the data gathered and following the 'framework' as described by Ormston (3), using both a deductive and inductive approach, themes and patterns were identified.

After analysis, three main themes were identified, each containing subthemes: 'the use of resources', 'current management' and 'the need for change'. All participants mentioned the use of local CTM UHB guidance and most utilised the 'MicroGuide' app. Others additionally used The Renal Drug Handbook, British National Formulary, Summary of Product Characteristics, and advice from Kidney Disease Improving Global Outcomes. All participants relied heavily on CTM UHB guidance for the choice of an antimicrobial, but most deviated from these, and recruited other resources, including other healthcare professionals, to decide on an appropriate dose. This suggests sufficient information is contained in CTM UHB guidance surrounding the choice of drug but is lacking advice regarding the dose. Methods to monitor function varied; many relied on serum creatinine and estimated glomerular filtration rate calculations while others also considered urine output and skin turgor. Actions regarding choice of antimicrobial were consistent but there were differences concerning dosing. Pharmacists believed standard doses were more appropriate than dose reductions, but lower doses were preferred by doctors. All participants felt antimicrobial stewardship and potential nephrotoxicity were of importance when treating SA-AKI while others considered weight, age, and previous use of antibiotics. Inconsistencies also occurred with time to review the drug ranging from 12-72 hours. Variation in management was attributed to lack of specific guidance, resources used and level of experience. Participants highlighted the need for specific guidance dedicated to AKI dosing and monitoring renal function, research into new biomarkers for AKI and improved communication via electronic methods.

This study demonstrated that the treatment of SA-AKI is inconsistent, which could negatively affect patient outcomes, and explored the reasons behind these differences. The data has provided evidence that supports the need for further education of staff and the requirement to include additional information within current guidance in respect to monitoring renal function and antibiotic dosing in SA-AKI. This project, along with future research across different health boards with comparison of mortality rates of SA-AKI, could provide further evidence for the development of new guidance or practice standards that would likely result in improved patient outcomes.

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The Development of PROTACs for the Treatment of Alzheimer's Disease: Opportunities and Challenges

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Proteolysis Targeting Chimeras (PROTACs) introduce a potential novel therapeutic strategy for the treatment of Alzheimer's Disease (AD). The disease is characterised by progressive neuronal degeneration caused by aggregation of specific proteins, such as tau. Tau promotes the stabilisation and association of microtubules inside the brain, but in AD it becomes hyperphosphorylated and aggregated, forming neurofibrillary tangles, which damage the structure of the brain and cause the symptoms of the disease, including a loss of memory and cognitive function. PROTACs are heterobifunctional targeted protein degradation molecules which utilise the cell's machinery to internally degrade their target proteins within cells[1]. This provides a favourable and selective therapeutic strategy for the treatment of AD, especially considering the current lack of effective therapies, which only slow down disease progression at best. Despite this, PROTACs have limitations, which may hinder their clinical application in the future. Due to the aberrant proteins in AD being inside the brain, drugs that target the condition need to cross the blood brain barrier (BBB) to be effective. However, this poses major challenges in terms of drug discovery, pharmacokinetics, administration, and efficacy[2]. A rapid review was conducted, which highlights the current evidence and research behind the use of PROTACs to treat AD.

Medline (Ovid), EMBASE (Ovid) and Scopus databases were searched in this rapid review. The search included the search terms: ('Alzheimer*' OR 'Alzheimer's Disease' OR 'Dementia') AND ('PROTAC*' OR 'Proteolysis targeting chimera*' OR 'Molecular glue*' OR 'Targeted protein degradation' OR 'Targeted protein therapy' OR 'Targeted protein therapies'). The results of the search were screened against detailed inclusion and exclusion criteria to identify all relevant articles. These papers were critically appraised for their quality using a modified CASP checklist. Findings of other relevant studies, such as reviews, were included to support the findings of the main papers. Ten preclinical laboratory-based studies were identified and used in the final review. Data from the papers were presented in tables, which included information on the BBB permeability properties of PROTACs, as well as the key study characteristics.

The reviewed studies included both *in vivo* and *in vitro* experiments, performed on cell, rat or mouse models. Five studies assessed the BBB permeability of their PROTAC, with three of them predicting their molecule to be permeable *in vivo* and one *in vitro*. However, the results of this review find that further research examining BBB crossing mechanisms are necessary to understand and optimise PROTAC delivery into the brain. This represents a key challenge and requires more complex clinical trials which take a longer length of time than traditional, non-CNS targeted small molecule drug discovery[3].

This rapid review presents a prospective for the feasible future use of PROTACs as therapeutics. The results find PROTACs to be successful degraders of proteins specific to AD, particularly tau and GSK-3b. Importantly, most studies identify their PROTAC to have a high specificity for their target protein, illustrated by the PROTACs' low dissociation constant values. This presents a major advantage over traditional small molecules in terms of the low predicted off-target effects and signifies the PROTACs' therapeutic potential. PROTAC technology therefore enables the discovery of novel therapeutic agents, which have a unique ability to specifically target and degrade otherwise undruggable proteins. To address issues relating to bioavailability, pharmacokinetic profiles and routes of administration, various delivery methods have been proposed, including nanotechnology, which aims to improve drug stability and delivery into the brain. Obstacles to drug delivery into the brain must be suitably addressed before PROTACs are ready to progress to clinical trials in AD patients.

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Urinary Biomarkers for the Early Diagnosis of Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer and has a notably poor prognosis with a 5-year survival rate of approximately 10%. This high mortality rate can be attributed to diagnosis at later stage (typically stage IV) as patients are often asymptomatic in earlier stages[1]. Thus, there is a clear need to identify biomarkers of early PDAC which may subsequently lead to earlier intervention and improved outcomes. Urine is a stable biological fluid with a complex matrix that can be collected easily without the need for invasive techniques making it a preferable option to blood[2]. The aim of this review is to investigate the literature and determine whether there are urinary biomarkers that might be useful for identifying early-stage PDAC.

Four databases (Medline, Embase, SCOPUS and Web of Science) were searched between 3rd Oct and 22nd Nov 2023 to identify relevant papers which focussed primarily on urinary biomarkers for pancreatic cancer. 528 papers were identified and their abstracts subsequently reviewed using specific inclusion/exclusion criteria which resulted in 8 papers being selected for critical evaluation using a modified CASP checklist (table A1).

Biomarkers reported in these 8 studies reflected three major areas: (i) Volatile Organic Compounds (VOCs), (ii) urinary proteins (iii) and metabolites. VOC profiling using GC-IMS could differentiate between PDAC patients and healthy individuals with 94% specificity and 84% sensitivity ($p < 0.0001$ PDAC versus healthy controls). Urinary proteins LYVE1, REG1B and TFF1 levels were all raised in pancreatic cancer patients versus healthy patients ($p < 0.0001$). A 6-metabolite panel was identified consisting of Trigonelline, Glycolate, Hippurate, Creatine, Myoinositol and Hydroxy Acetone. Trigonelline, Glycolate, Hippurate and Creatine were significantly decreased in PDAC ($p < 0.001$). The study of porphyrin metabolites, Uroporphyrin and Coproporphyrin, revealed that PDAC patients had higher Uroporphyrin levels than the healthy group ($p = 0.014$).

Several biomarkers showed strong potential to be used as diagnostic markers for early PDAC including a panel of six-metabolites and specific VOC profiles which were associated with PDAC vs non-cancerous tissue. The three proteins (LYVE1, REG1B and TFF1) showed better efficacy combined in a three-protein panel especially in the PancRISK model, a regression model combining the three-protein panel with patient age and creatine. The PancRISK model alongside CA19-9, a carbohydrate antigen currently used for PDAC diagnosis, increased the specificity and accuracy of CA19-9 which was previously reported to be non-specific and elevated in other conditions[3]. Porphyrin metabolites although of potential interest were not found to be specific to PDAC as they were also elevated in bladder cancer. Further research is required to identify the cause of the heightened levels seen in cancer and to establish their connection to PDAC[4]. Overall, this review has highlighted a number of circulatory components that have potential to be used as biomarkers for early PDAC with further investigation.

Number of studies	Study Design	Total number of PDAC patients included in review	Biomarkers included
8	All case control	642	VOCs, Proteins, Metabolites, Metals, miRNA

Table A1: Summary of literature searching, 528 papers identified through an initial screen of the literature using specific search terms. Abstracts reviewed and CASP criteria applied resulting in 8 papers selected for review

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Evaluating the risk of local reactogenicity in a human following application of a Microneedle Array Patch (MAP) to the skin

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The skin is an important target for local and systemic delivery of many therapeutics. However, drug delivery by this route is challenged by the outermost skin barrier, the stratum corneum[1]. Microneedle Array Patch (MAP) is an emerging dosage form that physically disrupts the stratum corneum to facilitate minimally invasive delivery of active pharmaceutical ingredients (APIs) into the skin using micron-sized needles[2]. Because of their minimal invasiveness and their enhanced drug delivery potential, MAPs have received extensive attention and have been widely investigated[3]. Despite the progression of MAPs to clinical trials, there are still no clinically approved MAP products. While clinical trials have reported local reactions following MAP application, the risk (severity and likelihood) of local reactogenicity in humans is unknown. Some local reactogenicity (local site reaction) may be anticipated from this delivery platform[4]. Local reactogenicity can influence the willingness to use MAPs. Understanding the risk is important to ensure the effective clinical translation of safe MAP products and encourage their informed use. This review evaluates the evidence for the risk of local reactogenicity following MAP applications to humans in clinical trials.

ClincialTrial.gov, EU Clinical Trial Register, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ISRCTN, Australian New Zealand Clinical Trials Registry and Dimension AI were screened using keywords related to MAP to identify clinical trials that assessed MAP application to the skin in human subjects. Local reactogenicity was identified as any application site reactions such as redness, swelling and oedema following MAP applications. Data extracted from the trials included trial descriptions, participant details, MAP characteristics and reported data on local reactogenicity (type of reaction encountered and the number of participants affected). These data were analysed to assess the prevalence and severity of MAP-related local reactogenicity across the included studies.

The search strategy identified 15 clinical trials of interest. Of the 15 trials involving at least 117,517 MAP applications in 1,543 participants, 8 trials reported local reactogenicity. These accounted for at least 116,767 MAP applications in 1,275 participants. 9 different application sites reaction were encountered. Erythema, oedema and haemorrhage were the most prevalent application site reactions experienced, with erythema being the most predominant (Fig A1).

The clinical evidence suggests that the application of a MAP to the skin may induce some mild, self-limiting local reactogenicity. However, the number of participants (1,543) and MAP applications (at least 117,517) investigated for local reactogenicity was limited and not extensive enough to reach a definitive conclusion. The clinical translation of MAPs has proven challenging. At present, patient and practitioner confidence in MAP products is likely to be key to the success of this dosage form. An evaluation and transparent communication of expected local reactogenicities is needed to address MAP hesitancy and guide its integration into clinical practice. Further studies are needed to expand upon current findings and fill the literature gaps to expedite the clinical translation of safe and effective MAP products.

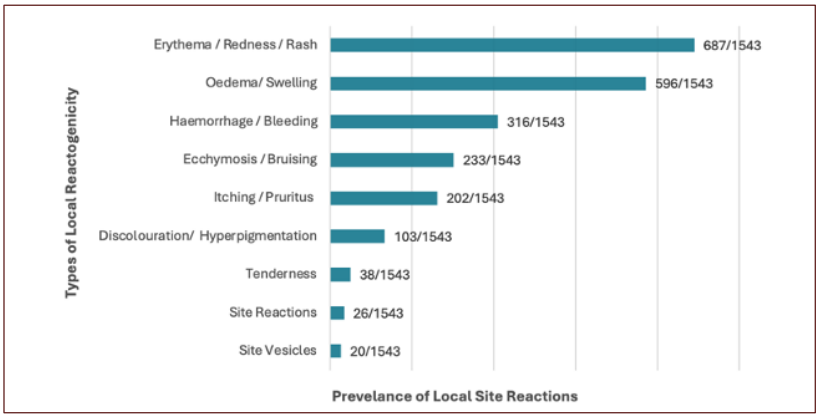

Fig. A1: Types of MAP-induced local reactogenicity and their overall prevalence across the 15 clinical trials studied.

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An investigation into the factors that have increased the use of doxycycline in primary care settings within the Aneurin Bevan University Health Board

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Antibiotics have been pivotal in the treatment of disease for decades, allowing what were once fatal infections to become more easily treated. In recent years, the combination of inappropriate prescribing methods and the improved ability of bacteria to adapt their defences has resulted in antimicrobial resistance (AMR). By 2050, AMR is expected to result in 10 million deaths per year1. Due to these alarming statistics, the UK government issued a 5-year action plan in 2019 to enable the issue of AMR to be tackled from the forefront2. Within Wales in 2022/23 tetracyclines, primarily doxycycline were the most prescribed antibiotic in terms of average dose prescribed, with 33% of all antibiotics prescribed (Defined daily dose/DDD)3. The Aneurin Bevan University Health Board, (ABUHB) had the second highest antimicrobial usage in Wales in Q4 of 22/23, with doxycycline being the second most used antibiotic from Q1 of 18/19 to Q4 of 22/233. Public Health Wales reports that doxycycline currently has an average course length, expressed as an items/DDD ratio, of 11.93 – based on NICE guidelines, this should be closer to 6-84. This study aims to investigate the prescribing of doxycycline within the ABUHB.

The study investigates prescribing data of 4 GP surgeries within the ABUHB, from November 2022 to January 2024. Included in anonymised data, were the gender and age of patients, the dose and strength of capsules and information regarding the rationale of prescribing. Only doxycycline 100mg capsules were analysed. Ethical approval was not required. The GP surgeries were selected using purposive sampling to assess the practice of surgeries at both extremes of prescribing numbers. Data for the socioeconomic status and general health of the population surrounding the GP surgery was obtained using the Office for National Statistics and the Welsh Index of Multiple Deprivation. Statistical analysis was performed using SPSS (v29.0.1.1). The descriptive statistics of the data were determined for each surgery and compared using Kruskal-Wallis statistical tests.

Surgery 4 had to be excluded from the analysis due to extensive errors regarding missing information and duplicated data that were impossible to resolve. The study compared doxycycline prescribing patterns across 3 GP surgeries. 647 patients were analysed (S1 n = 246, S2 n = 195, S3 n = 206). The mean number of capsules per prescription at surgery 3 was 20.50 (SD = 22.34), 17.62 (SD = 17.96) at surgery 1 and 10.29 (SD = 7.096) at surgery 2Fig 1. The data was not normally distributed (Shapiro-Wilk, $p<0.001$) A Krukal-Wallis test revealed significant differences in the number of capsules per prescription between Surgery 1 and Surgeries 2 and 3 ($\chi2(2) = 42.809$, $p = <0.001$). Repeat prescriptions were highest in surgery 1 (33.7%), followed by surgery 2 (26.2%) and surgery 3 (24.3%). The most common indications in Surgery 1 and 2 were respiratory conditions (S1 = 67 prescriptions, S2 = 83 prescriptions). In surgery 3 skin conditions were the most common (S3 = 57 prescriptions. Surgery 1 was the most deprived (in 20-30% of most deprived areas) and the highest number of residents in bad or very bad health (8.5%)4. The results of the study help to provide context as to how doxycycline is used with the ABUHB, and that external factors such as deprivation can be drivers of inappropriate usage. Overall, reporting accuracy needs to be a key focus moving forward - errors in duplication of patient data and reporting contribute to longer average course lengths.

	Surgery 1	Surgery 2	Surgery 3	Total
Number of capsules prescribed	473	303	345	1163
Mean number per prescription	17.62	10.59	20.50	19.33
Std. deviation	17.96	7.096	22.34	20.703
Min	1	4	6	1
Max	100	56	168	168

Figure 1: Quantity of capsules prescribed and the mean number per prescription

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Investigating the adherence of clinicians in Cardiff and Vale University health board to the prescribing guidelines for intravenous iron in patients undergoing haemodialysis

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Chronic kidney disease (CKD) is a long-term health condition characterised by a progressive decline in kidney function. This disease gives rise to many complications, anaemia being a prominent and complex issue amongst them. Anaemia is classed as a deficiency in red blood cells or haemoglobin. A major contributing factor to the development of anaemia is iron-deficiency, which causes low haemoglobin levels and subsequently a lack of oxygen-rich blood. Another cause is due to reduced erythropoietin production by the kidneys which results in a deficiency in red blood cells[3]. This condition can precipitate many symptoms such as fatigue and weakness, which reduce quality of life and increase the risk of morbidity and mortality. Haemodialysis (HD) involves some blood loss, meaning that patients have higher iron requirements than other renal modalities. HD provides an opportunity to directly introduce intravenous iron agents into the bloodstream to replete iron levels.

In December 2020, Cardiff and Vale UHB Nephrology and Transplant Pharmacy Service updated the guidelines on prescribing intravenous iron, with respect to the 'PIVOTAL' trial[2], which emphasised the superiority of a high-dose iron regimen compared to a low-dose regimen. The trial emphasised that a high-dose iron regimen decreased mortality and the risk of major cardiovascular events occurring. Despite the implementation of new guidelines, there are still incidences of patients having suboptimal iron levels, and cases of patients being iron-overloaded (receiving too much iron), which has raised concerns around compliance to these guidelines. Here, a quantitative data analysis is conducted to investigate the adherence of clinicians in Cardiff and Vale to the intravenous iron prescribing guidelines[1], to ultimately ensure patients are receiving safe and effective treatment.

A quantitative analysis of Vital Data Renal software from Cardiff South haemodialysis unit was undertaken for this research project. It involved looking at patients' iron biomarkers: TSAT, Ferritin, and Haemoglobin levels, from a seven-month period (April to October 2023), along with their iron prescriptions over this period. This information was then cross referenced to the guidelines to determine if guidelines were being followed.

From the 62 patients in this cohort, there were a total of 288 monthly reviews which included blood test results for each patient. Not every patient had reviews for every month of the seven-month period as some were introduced a few months into the study period which is when they started on iron treatment. Amongst these reviews, 224 of them preceded to follow the guidelines and prescribe the correct dose according to blood results, whilst 64 deviated from them. The majority of cases were due to doses being too high (58), and the remainder (six) were due to the doses being too low for patients' requirements. 17 patients were temporarily out of guidance for one month only before the dosing regimen was rectified, and 15 patients had consecutively more than one month where their dosing regimen deviated from the guidelines. This left a total of 30 patients who were consistently dosed correctly through the analysis period.

Furthermore, the data showed that 17 patients' dosing regimens only deviated from the guidance for one month before being changed appropriately, indicating that errors were quickly remedied, and it could have simply been an oversight. The remaining 15 patients who were consistently prescribed the wrong dose indicates that sometimes it is more than just an oversight. A major issue appears to be that blood tests aren't being completed in time for the consultant to undertake a monthly review, therefore they have to base their prescribing decision off the previous month's blood results which are not up to date and reliable. Some patients have also been on the same dose of iron for months or even years, therefore there may be a degree of reluctancy to change a dose that has previously worked for them. Despite prescribing matters, it is crucial to acknowledge that administration is a separate issue to prescribing. Even though prescribing may have been correct, some patients didn't have iron administered on some occasions due to presence of infection, admission into hospital, and refusal of a dose. These findings emphasize the importance of ongoing blood monitoring, personalised adjustments, and education to ensure the prescribing guidelines are followed consistently.

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A rapid review examining the role of Pyk2 in glioblastoma

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Cancer cells are characterised by unrestrained proliferation, migration and invasion are contributing characteristics resulting in patient mortality. A cancer subtype where this is particularly important is glioblastoma, due to its highly aggressive nature and being classified by the World Health Organization as a tumour with the highest level of malignancy[1]. Lack of funding, research, and biological sophistication have potentially led to the poor prognosis of the disease. Although being the most common primary tumour in the central nervous system, it presents with an average survival rate of only 12-15 months after diagnosis[2]. This creates a pressing need for novel therapy options. Proline-rich tyrosine kinase 2 (Pyk2) is a member of the focal adhesion kinase (FAK) family. It is known to be involved in factors which control adhesion, migration, and survival. However, the extent of involvement is understudied as a recent area of research, particularly in glioblastoma. Here, a rapid review is conducted to explore the relevance of Pyk2 in glioblastoma metastasis biology. This is observed through direct involvement, signalling indications that may imply a role in migration, as well as therapeutic efficacy of novel therapies targeting Pyk2.

Following PRISMA, databases Embase, Emcare, Medline, PubMed and Scopus were searched for MeSH terms related to and including ‘Cancer’ AND ‘Glioblastoma’ AND ‘Pyk2’. Studies identified were then subject to extensive inclusion and exclusion criteria prior to critical assessment using a modified CASP framework. Articles that demonstrated an insight into the role of Pyk2 in glioblastoma specifically, were included in this rapid review, and ones that present downstream signalling indications were taken on for further assessment.

Eleven publications met the inclusion/exclusion criteria and were taken on for further assessment. Significantly, all but one of the papers showed a correlation between increased Pyk2 phosphorylation and increased glioblastoma migration. An array of data collection methods was utilised, both in vitro and in vivo. Significant results were gathered from western blot analysis to assess activation and expression levels of the relevant proteins, and rat/mice intracranial xenograft models to assess outcomes. The N-terminal FERM domain was identified by multiple studies as a promising alternative target to inhibit migration compared to kinase inhibitors, with the binding partners MAP4K4 and 12A10 scFv proving to have inhibitory characteristics to this domain. Pyk2 was seen to impact migration directly, and through acting as a signalling scaffold for pro-migratory activation of further kinases. This was mainly through downstream involvement in the store-operated calcium entry (SOCE) and HCMV pathway. The studies introduced the idea of co-treatment of anti-VEGF treatment with a Pyk2 inhibitor to improve efficacy in response to the hypoxia-induced mechanisms leading to increased Pyk2 expression.

Although closely related, it was found that FAK and Pyk2 work independently of each other. FAK is associated with high proliferation and low migratory rates, whereas the opposite is seen with Pyk2. Furthermore, FAK inhibitors can selectively inhibit FAK but not Pyk2, and still not influence glioma cell migration. This highlights the key role of Pyk2 in being responsible for inducing glioblastoma via migratory pathways, and the importance of future research into novel therapy. Traditional kinase inhibitors are associated with reduced selectivity, potentially impacting drug efficacy in targeting the desired signalling pathway. Therefore, the FERM domain presents as an appropriate alternative which the efficacy as a target was shown in effective inhibition of migration throughout this review. With improved specificity in this domain, direct inhibition of Pyk2 would also target downstream signalling and the issue of tumour regrowth following surgical resection. An additional study presented the same correlation between Pyk2 expression and migration in medulloblastoma. This further increases viability of further research into Pyk2 as a promising target, as it may have a universal role across tumours of the central nervous system.

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Service user feedback on the interaction with prescribers in primary care: a scoping review

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Pharmacists' ability to prescribe certain medications began with supplementary prescribing in 2003, which enabled pharmacists to collaborate with doctors on patient treatment plans[1]. In 2006, amendments to the Medicines Act established independent prescribing, allowing suitably qualified pharmacists to prescribe within their competence without a doctor's diagnosis, which was first implemented in Wales in 2007[2]. Welsh healthcare initiatives in 2018 prompted the Welsh pharmaceutical committee's publication of "Pharmacy: delivering a Healthier Wales", setting goals including having "one pharmacy independent prescriber in every community pharmacy in Wales by 2030"[3]. This facilitated the piloting of the independent prescribing service (IPS) in community pharmacies in 2020. Since the piloting, the IPS has become part of the pharmacy contract, meaning any pharmacy in Wales will be able to provide the service. This aligns with government objectives to enhance primary care, ease pressure on GPs, and reduce hospital admissions through a unified healthcare system. Due to the IPS being new, there is a lack of literature focussing on it. Therefore, there is a need to obtain service user feedback in order to improve the quality of care and service delivery and help inform practice. A focus on different prescribers within a primary care setting is necessary to ensure a wide range of information is gathered due to the paucity of literature focusing on only community pharmacy. This scoping review, therefore, aims to explore service user feedback within the literature on the interactions with prescribers in primary care and identify information related to sampling, recruitment strategies and types of questions to explore in order to aid the wider research aim. The wider research aims to explore patient feedback on the independent prescribing service provided by community pharmacies in Wales.

This review was based on the recognised framework for scoping reviews by Arksey and O'Malley[4]. The search terms were identified following the Population, Concept, and Context (PCC) framework and inclusion and exclusion criteria were set. Examples of some search terms identified and used are "primary care", "prescrib*" and "feedback" with a focus on peer-reviewed papers in the English language. Subsequently, papers were systematically retrieved from comprehensive databases, including Web of Science, Medline (Ovid), CINAHL, and Scopus. Duplicates were removed using Endnote to ensure data integrity. Initial screening of titles and abstracts was independently conducted by two reviewers, adhering to predefined exclusion criteria. A subsequent screening phase involved two reviewers' independent assessment of each article's full text, ensuring a meticulous and robust selection of relevant studies. Relevant information was extracted into a data extraction table, and thematic analysis was employed to identify themes.

The initial search identified 567 papers (2003-present), 341 after duplicates were removed. Following a thorough screening process, 20 papers that met the inclusion/exclusion criteria were selected for analysis. These papers investigated the perspectives of service users interacting with various healthcare professionals, including GPs, pharmacists, and nurse prescribers, across diverse primary care settings such as GP surgeries, community centres, health authorities, and community pharmacies throughout the United Kingdom. The feedback gathered from service users in these papers encompassed several common themes, including patient satisfaction, consultation duration, access to care, alignment of agendas, confidence in prescribers, as well as the communication style, approachability, and thoroughness of prescribers during patient interactions. There were also themes identified within the sampling strategies, such as purposive and random sampling, as well as recruitment strategies, such as the use of gatekeepers, postal recruitment and different prescribing networks being used to recruit patients.

The recommendations from the scoping review suggest that the areas of key interest to the wider research team for gathering feedback from service users on the IPS are surrounding the themes of communication, consultation duration, access to care and overall service user satisfaction with the service. Regarding the methodology and recruitment, suggestions and recommendations have been identified, such as the use of prescribers as gatekeepers in recruitment. However, the project needs to review the wider literature in general for potentially more appropriate sampling methods, such as census sampling of every service user within a given time frame. This would reduce the risk of selection bias identified in some of the papers included in this review. Consultation with relevant stakeholders would also be needed to help inform the project to ensure that the wider research aim is met.

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Sink contamination in the intensive care unit (ICU), contributing factors and associated burdens: A rapid review

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Although sinks are commonly viewed as necessary components of hospital ward design, recent research has suggested they may cause more issues than they solve. Sinks harbour high risk pathogens within their faucets and drainage systems, which can go on to infect or colonise patients with multi-drug resistant organisms[1]. This review aims to provide a summary of key elements of research, and what the research found and highlighted.

Search engines, Scopus and Ovid:Medline were used in accordance with PRISMA guidelines, using the terms 'sinks' OR 'handwashing sinks' AND 'ICU' OR 'intensive care unit'. Any papers published before 2015, or whose focus was neonatal ICUs were excluded, leaving 19 papers included in the review.

All papers based their findings on pathogens rated Priority One – Critical by the World Health Organisation (WHO)[2], suggesting these pathogens are more likely to be found in the sinks of ICUs, and thus be spread to critically-ill patients. Antibiotic susceptibility testing was also employed in 74% of the papers. Within this, all pathogens identified displayed multi-drug resistance, further emphasising the importance of tackling contaminated sinks. 63% of papers evaluated the role of biofilms within the sinks. Although biofilm mention in each paper was brief, many highlighted the ability of biofilms to maintain sink colonisation, despite disinfection efforts. Klebsiella pneumoniae and Pseudomonas aeruginosa were commonly identified within sink environments, both "Critical" pathogens, due to their ability to exhibit multi-drug resistance, therefore making them harder to treat[3]. 42% of articles included were conducted over known outbreak periods. There were various definitions of 'outbreak', which caused issues when comparing outbreak protocols between the literature. Most conducted within outbreaks acted by removing or replacing the sinks in the ICU, controlling the outbreak and preventing the spread of disease, further supporting the fact that sinks are reservoirs for pathogens.

Overall research suggests contamination of sinks in ICU is a constant recurring problem and does not differ in severity during both outbreak and non-outbreak periods. Contamination of multi-drug resistant pathogens is frequent which may not be susceptible to many available antibiotics. New protocols should be suggested in order to limit or stop this, such as the removal of sinks and the introduction of water-free patient care, which has been trialled and shown success in early research[4].

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Investigating the effects of arrhythmia-linked calmodulin variants on the phosphoregulation of the cardiac ryanodine receptor

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Calcium (Ca^{2+}) signalling is integral for cardiac muscle contraction. In the cardiac myocyte, the action potential elicits Ca^{2+} entry into the cell through voltage gated Ca^{2+} channels. This in turn activates cardiac ryanodine receptor Ca^{2+} release channels (RyR2), situated on the sarcoplasmic reticulum (SR), evoking the massive

Ca^{2+} release event which culminates in contraction. Studies have correlated alterations in the RyR2 signalling macromolecular complex to functional cardiac abnormalities, such as arrhythmia, some which can result in sudden cardiac death. The accessory protein calmodulin (CaM) forms part of this complex with RyR2[1]. CaM is a multifunctional Ca^{2+}-binding signalling protein, known to modulate RyR2 function via two mechanisms. One mechanism is to directly bind to RyR2, inhibiting Ca^{2+} release; the second is via activating CaM kinase (CaMKII), which phosphorylates RyR2, increasing RyR2 activity[3]. Some CaM mutations have been associated with altered RyR2 function, leading to the arrhythmia syndrome catecholaminergic polymorphic ventricular tachycardia (CPVT)[4]. This study will be focusing on two novel CPVT associated CaM mutants, D132E and Q136P, compared against wild-type (WT) CaM, investigating if these mutations cause a significant change to RyR2 phosphorylation, and thus, changes to Ca^{2+}release, which could lead to arrythmia[5,6].

In this project, the effect of CaM mutation on activation of CaMKII was assessed using a phosphorylation assay. Binding CaM leads to CaMKII autophosphorylation, which activates the kinase[3]. This was assessed using an in vitro reaction containing purified recombinant CaMKII in the presence of either WT or mutant CaM at time intervals of 0s, 30s, 60s, 120s and 300s. In addition to this, co-expression of RyR2 with WT or mutant CaMs in HEK293 cells was used to investigate the effect of mutant CaM on RyR2 phosphorylation levels at the CaMKII phosphorylation site (S2815). HEK293 cells were transfected with plasmid DNA encoding RyR2 and WT or mutant CaM, and harvested after 48 hours, before hypo-osmotic lysis.

Reaction samples from the CaMKII assay were analysed by SDS-PAGE and Western blotting using an antibody for phospho-CaMKII. Phosphorylation levels were normalised to total protein levels and analysed using One-way ANOVA statistical analysis. This revealed that while the D132E mutant showed comparable CaMKII activation to WT CaM, Q136P-induced autophosphorylation was significantly reduced ($p<0.05$), suggesting that this mutant is not as effective in activating the kinase. RyR2 phosphorylation at S2815 was analysed by SDS-PAGE and Western blotting where phospho-RyR2 levels were normalised to total RyR2 levels. One-way ANOVA statistical analysis was run and at $p<0.05$, these experiments found that RyR2 phosphorylation was equivalent for D132E and WT CaM but decreased in cells co-expressing Q136P CaM. This corroborates the results of the autophosphorylation assay, showing that decreased CaMKII activation by Q136P CaM, resulted in lower RyR2 phosphorylation.

Since phosphorylation of RyR2 plays a crucial role in its Ca^{2+} release function, Q136P CaM's effect may lead to changes in SR Ca^{2+} release, potentially acting as a pro-arrhythmogenic event in the pathophysiology of CPVT(2). However, due to CaM's multifunctional nature, and since the effect of this CaM mutant on this signalling protein's role in direct RyR2 inhibition has not been established, the mechanism of dysfunction is likely to be more complex, requiring further investigation.

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The safety of incorporating penicillin allergy history in de-labelling interventions by non-allergy specialists

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Penicillin antibiotics are essential for the treatment of bacterial infections. However, the use of penicillin is limited in patients with a penicillin allergy label on their medical record, and these patients are often prescribed penicillin alternatives such as macrolides (1). The use of penicillin alternatives is associated with increased incidences of antimicrobial resistance and Clostridium difficile infection (2). On testing most penicillin allergy labels are incorrect and can be removed from patient medical records (3). The removal of allergy labels is referred to as allergy de-labelling and is often completed by allergy specialists/allergists (3). Penicillin allergy de-labelling by non-allergy specialists in hospital settings has been supported with the release of guidance for

practitioners (4), although implementation of de-labelling in primary care is limited. Primary care practitioners have stated their concerns about the training required for penicillin allergy de-labelling and the safety of de-labelling interventions (5). The aim of this rapid review is to present the outcomes of penicillin exposure in patients who have been directly de-labelled, or risk stratified as suitable for oral provocation challenge based on allergy history by non-allergy specialists and comment on the safety of this practice.

A rapid review approach was adopted. A systematic literature search was conducted November 2023 and repeated January 2024. A database search of EMBASE (Ovid), Emcare (Ovid), Medline (Ovid), SCOPUS and Web of Science was completed using set search terms. Search terms were in the form of key words and subject headings. Handsearching citations of a systematic review was completed to identify references not obtained from the database search. Titles and abstracts were screened against the set inclusion/exclusion criteria and selected full texts were assessed for eligibility. The studies were grouped based on their interventions and context of penicillin exposure. Data extraction of the eligible full texts was completed to answer the research question. The eligible studies were critically appraised using selected critical appraisal tools to identify bias and assess the quality of the studies.

Eleven publications of a good quality were selected for inclusion. Four studies de-labelled patients based on allergy history to optimise antimicrobial therapy in the hospital setting, and nine studies used direct oral provocation challenges to de-label participants with penicillin allergy labels. Non-allergy specialists included pharmacists, physicians, and nurses. Most de-labelled patients/participants tolerated penicillin antibiotics. However, there were reports of adverse events and re-labelling of penicillin allergies following penicillin exposure. Two adverse events were reported in the 40 directly de-labelled patients who received penicillin and eleven adverse events were reported in the 359 participants who received an oral provocation challenge. No study reported an incidence of a clinically severe allergic reaction following penicillin administration in their cohort.

Studies that comment on direct de-labelling show non-allergy specialist hospital teams can de-label penicillin allergy. There were only four hospital-based studies that directly de-labelled penicillin allergy, highlighting the need for studies to be completed in primary care. Nine studies de-labelled participants by direct oral provocation challenges, most participants tolerated penicillin challenges following risk stratification based on their allergy history. A small number of participants reacted to challenges or subsequent penicillin exposure, as seen in studies that risk stratify by skin testing where positive oral challenges occur following negative skin tests. The studies in this review provide evidence allergy history can be incorporated into de-labelling interventions used by non-allergy specialists to de-label patients with a penicillin allergy. Non-allergists can use these interventions in hospital settings, but evidence of safety is needed from primary care to make a valid recommendation for this practice.

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Strategies to enhance the racial and ethnic diversity of breast cancer clinical trials: the development of the Racial Minority Growth (RMG) Model

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Randomised double-blinded clinical trials (CTs) are ‘gold standard’ research studies, where new therapeutics, including breast cancer (BC) therapies, are rigorously evaluated in humans. CTs are designed to ensure drugs are safe and efficacious, so the populations included should be representative of the wider BC patient population. Often this is not the case (1,2). A 2021 Journal of Clinical Oncology review identified 12 major BC trials where 2.1% of participants were Black, 3.7% Hispanic and 15.5% Asian, all much lower than the wider United States minority population[1]. Better BC trial diversity is needed for a variety of reasons, including patient safety and pharmacogenomic (PGx) consequences. PGx considers how genetics can influence drug

response, and trials that fail to include minority patients could overlook their different genetic makeup, impacting drug pharmacokinetics in particular[2]. In 2022, the US Food and Drug Association mandated an increase in 'underrepresented racial and ethnic populations' in CT[3]. This rapid review responds by reviewing and presenting a set of evidence-based strategies that could diversify BC trials, create safer drugs, and enhance patient and provider confidence.

A rapid review approach was used, searching Medline, Embase and Scopus. Clear inclusion and exclusion criteria were set, and search terms surrounding 'racial diversity', 'breast cancer', and 'clinical trials' were used. In this context, REM refers to minority groups other than the non-Hispanic White population who are often well-represented in CTs[3]. A PRISMA diagram documented the screening process, and a modified CASP checklist aided critical appraisal. Eight main strategic themes were extracted to form a results table, and the Racial Minority Growth Model (**Fig 1**).

Seventeen papers met inclusion/exclusion criteria; five randomised controlled trials, five reviews, four interviews, two cohort studies and one case-control study. Studies using multi-pronged interventions were the most successful. This was supported by REM feedback, suggesting efforts should acknowledge that participation is nuanced and multifactorial. The most prevalent theme was making appropriate cultural accommodations, for example using cultural competence models to adapt job roles. BC patients emphasised the importance of engaging with community members and having better representation of minority researchers and healthcare professionals to address mistrust.

It is not surprising multiple strategies are needed, when there are many barriers to access[2]. Alongside this, each REM group will have different social, religious, and economic circumstances that shape their decisions. It is questionable how applicable the results are to REMs in all geographies, for example US safety-net clinic versus UK's National Health Service. One strategy will not fit all. Due to the review's limitations, the use of the model as stand-alone strategy is cautioned. It should be used as starting point, alongside other models to inspire the diversification of BC trials and other therapeutic areas. Future work should implement RMG-inspired strategies in hypothesis-driven research to assess practicality and effectiveness, with a focus on retention. Funding was a clear driver of success, which future policies should acknowledge. The model could inspire the role of a pharmacist oncology navigator, aligning with nurse navigation models seen in the studies. Pharmacists, often based in the community, have established patient relationships, and could therefore act as cultural brokers to support diversification. Pharmacists have been invaluable to recruitment of trials in the wider field, and their involvement has the potential to become standard practice[4]. In summary, this review was successful in identifying multiple strategies that could diversify BC trial populations, in response to the clear and urgent need to focus increased attention on the medical needs of REM populations.

Figure 1: The Racial Minority Growth (RMG) Model

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Exploring the financial and operational impact and views of patients of prescribing ESA medication on WP10HP prescriptions for people with kidney disease across South West Wales

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Anaemia can be a complication of Chronic Kidney Disease (CKD) and it occurs due to reduced production of the hormone erythropoietin in the kidney. Erythropoiesis-stimulating agents (ESA) can be used to treat this and improve the quality of life and general well-being of patients with anaemia in CKD[2]. This medication is currently prescribed on a hospital prescription and supplied at a negotiated contract price. As ESA prescriptions are currently supplied against a hospital prescription, they are subject to VAT. However, ESAs have now been added to the primary care rebate scheme so they can be prescribed and dispensed on a WP10HP prescription and this will be VAT exempt leading to potential cost savings for the NHS[1]. This study aims to determine whether prescribing ESA on a WP10HP prescription in South West Wales could be more cost effective than prescribing and dispensing in hospitals and to capture the opinions of patients who are eligible for this change. The concerns of the patients will be noted as well as the benefits and problems with this switch.

A combination of qualitative and quantitative methods were used. A focus group was conducted. Study participants (N=3) were patients of the renal department at Morriston Hospital and were currently taking ESA injections. Thematic analysis was conducted on the transcript to identify themes. Patient cohort data (n=365) provided by Morriston Hospital was also analysed. This included age, sex, first part of home postcode, frequency and type of ESA used, method of administration, delivery status, number of prescriptions collected and closest clinic for collection.

The switch from hospital to WP10HP prescription could result in a significant cost saving of £18,396.07 per year for the renal team at Morriston Hospital. However, there are other operational impacts that need to be taken into consideration. The mean average distance travelled to nearest clinic for the 356 patients provided in the data set for one journey was 15 miles. However, the mean average distance to a community pharmacy was significantly less at 1.71 miles. Patients from rural areas would prefer to collect from their local community pharmacy because it would reduce the distance travelled significantly. Also, patients collect repeat medications from their local pharmacy so collecting their ESAs at the same time means no extra travel is required. However, participants had other concerns regarding the level of expertise of community pharmacists, supply issues, waiting times, storage space and how quickly dose changes are dealt with in a community pharmacy.

Patients had varied responses to this proposed change. Although, the distance needing to be travelled is significantly less, the patients raised other concerns such as their confidence in community pharmacies and the uncertainty of how many injections will be given per prescription. This could lead to lack of storage space in the patients' fridges. Many patients are comfortable receiving the injection from the hospital and value seeing the renal team face to face. Also, ESA doses may fluctuate because haemoglobin levels can vary due to several reasons such as infection, chronic inflammation, co-morbidities medications, nutritional status etc[3]. These dose changes may not be resolved quickly in a community pharmacy. Furthermore, whilst there is a significant cost saving for the renal department, the NHS would have to pay pharmacy contractors fees such as the dispensing fee and expensive item fee[4]. Therefore, this cost saving for the NHS may not be as significant; it is essential that rebate schemes should have an economic benefit to the NHS. In conclusion, this proposed change presents several problems which will need to be addressed. However, this change is suitable for certain patients who are on stable doses, from rural areas, working 9-5 or over the age of 70.

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Investigating the Impact of Menopause on the Risk of Depressive Illnesses and Suicidal Ideation: A Rapid Review of the Literature

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Menopause is a natural physiological transition inherent to all women, typically occurring between the ages of 45 and 56, marking the end of their reproductive years. During this transition, the production of oestrogen by the ovaries begins to decline, commonly resulting in well-known physical symptoms, such as hot flushes and night sweats[1]. Hormonal fluctuations may also trigger a variety of psychological symptoms as oestrogen plays a vital role in regulating serotonergic activity[2]. Thus, a hypothesis emerges suggesting a potential link between diminishing oestrogen levels and an elevated incidence of depressive symptoms. Despite the known detrimental effects poor mental health can have on an individual's quality of life, limited research has been conducted focusing on how menopause may contribute to depressive symptoms, particularly those associated with suicidal ideation and disturbances in daily functioning. During this phase of midlife, women in the United Kingdom experience their highest suicide rates[3], which alerts us to think about contributing factors, including fluctuating oestrogen levels, socio-economic changes and lifestyle stresses at this time. A rapid review has been conducted to answer the research question, 'To what extent does menopause influence the prevalence of depressive disorders and suicidal thoughts among peri- and post-menopausal women?'.

A rapid review methodology was adopted, where databases, Medline (Ovid), Embase (Ovid) and Scopus, were searched for 'menopause' AND 'depressive illnesses' AND 'suicide'. Further studies were identified by reviewing references within the selected papers. Nine papers met the clearly defined inclusion/exclusion criteria and underwent critical appraisal using the modified checklist for cohort studies from the Critical Appraisal Skills Programme to assess both relevance and quality of results. These studies examined the incidence of depressive symptoms during menopause, with suicidal ideation being the primary outcome measured in all papers.

The collective findings from nine studies of high to moderate quality taken forward for review, shed light on the complex relationship between menopause and depressive disorders, particularly in relation to suicide risk – a significant global health concern. All studies used questionnaires or interviews from surveys to assess suicidal ideation. Five studies investigated the effects of early menopause, whether natural or due to surgical interventions such as oophorectomy[4], whilst three studies compared suicidal ideation rates between women in different phases of the menopausal transition. Outcomes of suicidal ideation were higher in those who had undergone early menopause, however, there were discrepant findings among studies looking into the menopausal stage at which suicidal ideation is highest. Two studies reported that postmenopausal women were identified as being at the highest risk of suicidal ideation, while another two studies found perimenopausal women are most vulnerable.

Despite the overarching consensus that peri and postmenopausal women face increased risk of suicidal ideation compared to premenopausal women, a risk that is amplified in women who experienced early menopause, the presence of divergent results among studies exploring depressive symptoms across different menopausal stages, alongside the outcome of another study reporting no significant findings, highlights the need for further investigations. Longitudinal studies, following large cohorts of women, are crucial to understand the complex effects that fluctuating hormone levels and changing social dynamics, have on women's mental health at the time of menopause, which current research does not yet adequately address. Moreover, the included studies, mostly cross-sectional in design and focused on Asian populations, have limitations in terms of small sample size and potential bias due to non-random sampling. Caution needs to be taken when applying these conclusions universally, especially considering that female suicide rates in South-East Asia remain higher than those in the West. Nevertheless, after considering these precautions, the findings aim to inform healthcare professionals on proper identification and management of depressive disorders in menopausal women before severe manifestations of low mood lead to suicidal tendencies.

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Exploring Selective Inhibition of GRK 1 as a New Therapeutic Intervention for Retinitis Pigmentosa

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Retinitis pigmentosa (RP) is an inherited blinding condition that affects 2.5 million people worldwide.1 Current treatments are inefficacious and a cure for the condition has not yet been developed. Several genetic mutations result in molecular disturbances of the visual cycle, progressively affecting the field of vision, causing RP. Retinal degradation results in progressive narrowing the patient's field of vision over time, until central vision is completely lost.2 Class-3 mutations to the RHO gene, which encodes for the rhodopsin protein, result in a particularly severe and fast-progressing form of RP. These mutations enhance rhodopsin's phosphorylation by G-protein-coupled kinase 1 (GRK1), the rhodopsin kinase. Hyperphosphorylation interrupts the recycling process of rhodopsin in rod photoreceptor cells, leading to their death.

To resolve the molecular disturbance caused by class-3 mutations, this study explores the possibility of selectively inhibiting GRK1, to reduce the hyperphosphorylation that result from rhodopsin mutation, thus enabling rhodopsin physiological recycling. The research was based on using a range of online tool and computer modelling software to identify selective inhibitors of GRK1. First, Uniprot was used to obtain protein sequences for each human kinase of the GRK sub-family, GRK1-7. Using these sequences and the Protein Data Bank (PDB), 3-D structures for each kinase, or suitable homologous structures to be used as a template, were obtained.4,5 For those kinases which did not have a 3-D structure deposited in the PDB, structural models were built by homology modelling. On top of comparing the primary sequences of GRK1-7 using BLAST, their 3-D structures were analysed to compare the active site of GRK2-7 to the active site of the GRK1 model, enabling the identification of which human GRK is most similar to GRK1.2,3 A comparative virtual screening analysis of the Specs library of commercially available, drug-like small molecules was then run on the active sites of both kinases, to select potential selective inhibitors of GRK1.

Active site analysis revealed GRK7, the kinase of cone opsins, shared the greatest structural similarity, as well as sequence identity, with GRK1.2 However, significant differences in amino acid composition between their active sites were identified (Figure 1), raising the potential for the development of a selective GRK1 inhibitor. A docking-based virtual screening analysis of the Specs library was conducted on the active sites of both GRK1 and GRK7, to identify potential inhibitors predicted to selectively bind GRK1 with a higher preference over GRK7.3 The screening was conducted applying a molecular docking stage first, which generated predicted binding poses for ligands with a high affinity for each active site. The docking results were then rescored with three different scoring functions, according to a consensus scoring procedure optimised in-house. The best-scored ligands were chosen for both kinases, to produce a database of the entries with the best-predicted binding to each GRK. The two databases were combined, and shared entries were removed, to produce a database with the best solutions for the GRK1 site only (3004 entries). Each entry was visually inspected for binding interactions with GRK1 active site residues and overall occupation of the active site, enabling the selection of 14 promising ligands. The selected ligands will now be purchased from the vendor and evaluated in a panel of enzymatic and cell-based bioassays relevant to RP.

Patients with RP caused by class-3 rhodopsin mutations face a rapid decline in their field of vision, quickly progressing into total blindness. Selective inhibition of GRK1 may enable the development of an efficacious treatment to delay disease progression and slow down the narrowing of vision, by exploiting a selective GRK1 inhibition mechanism.

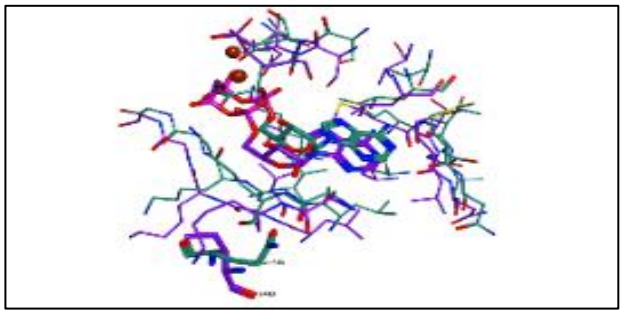

Figure 1: Active site comparison of the structures of GRK1 (carbon atoms in green) and GRK7 (carbon atoms in purple) with bound ADP.

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Elucidating a structural model for GATA2 to identify selective inhibitors and aid re ikaemia

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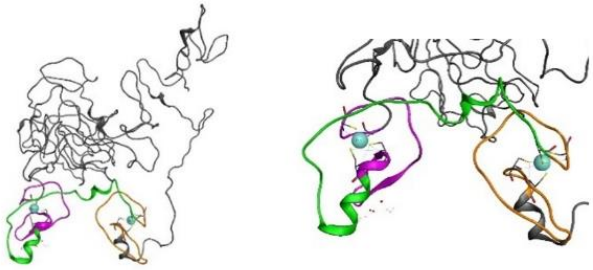

Figure 1. The image on the left is the complete final model chosen to undergo virtual screening. The image on the right is the same image zoomed in on the zinc fingers. The C-finger of GATA-2 is pink, and the N-finger of GATA-2 is green.

Acute myeloid leu fficult to treat because of the involvement o chemotherapy. Relapse occurs in half of a r these patients[1]. GATA-binding factor 2 (mising target for specific treatment of AML ve GATA2 inhibitors are available. Althoug characterised by two zinc finger domains, w

The aim of this work was to use computational methods to obtain a complete 3D structure for GATA2, to enable the identification of selective GATA2 inhibitors, which would stop DNA transcription occurring, causing apoptosis in AML cells.

The primary sequence of human GATA2 was downloaded from UniProtkb, and a BLAST search was run to identify human proteins with high sequence identity. A 3D model for GATA2 was then constructed using a combination of protein threading (I-TASSER) and homology modelling (MOE) approaches. The model was used for the structure-based virtual screening analysis of the Specs library of commercial, drug-like compounds. After an initial molecular docking stage, all generated binding poses were rescored using a combination of three different scoring functions, to select those molecules with the best predicted binding to the target site. The predicted drug-like properties of the best-performing compounds after visual inspection were evaluated using SwissADME.

After performing a BLAST search on the human GATA2 amino acid sequence, human GATA1, 3, 4, 5 and 6 were identified as the most similar proteins, and the zinc-finger domain was a common ligand binding site for all of them. The available crystal structure for GATA3 zinc-finger domains in complex with a DNA segment was used as a template to build the corresponding domains for GATA2 by homology modelling. The remaining portions of the structure were built by protein threading, and an energy minimisation of the final structure was performed around the bound DNA.

The zinc finger portion where the amino acid residues Arg307, Arg308 and Asp309 are located, which are known to be key for GATA2 activity in AML (3, 4, 5, 6), was used as a target site to evaluate the predicted binding of the small, drug-like compounds in the Specs commercial library, to identify potential GATA2 inhibitors. The entire library was evaluated with a fast docking simulation first, and the 10% best compounds were re-docked using a more accurate docking algorithm. After rescoring the output poses with a combination of three different scoring functions, molecules falling in the best 25% for two out of three scoring functions were visually inspected for their predicted binding to GATA2. After excluding compounds with reactive or toxic functional groups, molecules were clustered according to a similarity of 70%, and for each cluster the best binding molecule was chosen. Finally, SwissADME was used to prioritise molecules with good predicted drug-like properties, leading to a final selection of 42 compounds.

A three-dimensional structure was successfully obtained for GATA2 (**Figure 1**), which revealed a suitable binding area, corresponding to one of the zinc-finger domains, for selective GATA2 inhibition. This structure can now aid future research into the specific targeting of GATA2 with inhibitors of its binding to the DNA, with the promotion of cell death when this interaction is disrupted. As part of this work, following a structure-based virtual screening analysis of the Specs compound library on the GATA2 model, 42 chemically diverse potential inhibitors of GATA2 were chosen for laboratory testing, all showing an optimal predicted binding to the zinc-

finger target site in GATA2, and good drug-like properties. These molecules will now be purchased from the vendor and evaluated in different cell-based assays for their therapeutic effect against AML.

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Analysis of trends in prescribing and administration of centrally acting drugs in older adults living in care homes in Wales from February to October 2015

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Care homes provide support for older adults who may require assistance with daily activities of living whilst also ensuring a safe environment and a sense of community and independency. (1) Within these care homes, medicines related harm has been associated with inappropriate prescribing and administration practices (2). These trends have been prominent within the centrally acting drugs (3). Non-benzodiazepine hypnotics like Z drugs are commonly used for insomnia. The doses for an adult (7.5mg) and for an adult aged over 65 (3.75mg) differ, due to the ability of the drug to cause impairments such as dizziness and falls (4). Benzodiazepines should be prescribed for less than 4 weeks and in many cases, studies have shown that they have been prescribed for longer (2). Second generation antipsychotics are favoured over the first generation due to their lower side effect profile, which is preferred in older adults to prevent cognitive side effects (3).Our aim is to analyse data to gain insight into the trends of prescribing and administering seen within care homes and whether these errors can attribute to any harm to the residents.

In this study, 12 care homes were investigated within Wales between February and October 2015. The data was obtained through a database of prescribing and administration data from an electronic administration record system (eMAR). Extracted data from database included the care home and patient number, drug prescribed including strength, formulation and instructions on dosing regimen, time it is to be administered and when it was administered.

Throughout the whole study there were 328 residents, the average medicines prescribed over the whole cohort was 7.34 medications. In the 12 care homes 29 residents within the study were prescribed Zopiclone. Out of these 19 (65.5%) residents were prescribed the recommended dose of zopiclone for an older adult and 10(34.5%) were prescribed the adult dose. Benzodiazepines were prescribed for 55(16.77%) residents across all the care homes. Out of those 55 residents , 19(34.55%) of residents were prescribed the recommended duration (2-4 weeks) and 36 (65.45%) residents had prescribed them for longer than 4 weeks with a maximum of 247 days and a minimum of 1 day. Antipsychotics were prescribed for 64(19.51%) residents across all the

care homes. First generation antipsychotics were administered to 24(37.5%) of those and 40(62.5%) residents were prescribed a second-generation antipsychotic.

Overall, the data analysed shows that Zopiclone was prescribed according to the guidelines for most residents however, those that were prescribed the adult dose may have adverse effects which have been shown to affect cognitive processes and psychomotor functions. Residents that were prescribed were majority administered them for more than 4 weeks. Longer duration of benzodiazepines administered to patients have resulted in side effects including impaired thinking, memory loss and tolerance and dependence problems. Antipsychotics were mainly prescribed as second generation limiting the extrapyramidal side effects including sedation which can increase risk of falls and fractures. Overall, this study shows that prescribing can be improved within care homes to ensure that those taking these centrally acting drugs are less susceptible adverse effects that can impair their cognitive ability resulting in an increased risk of falls and fractures.

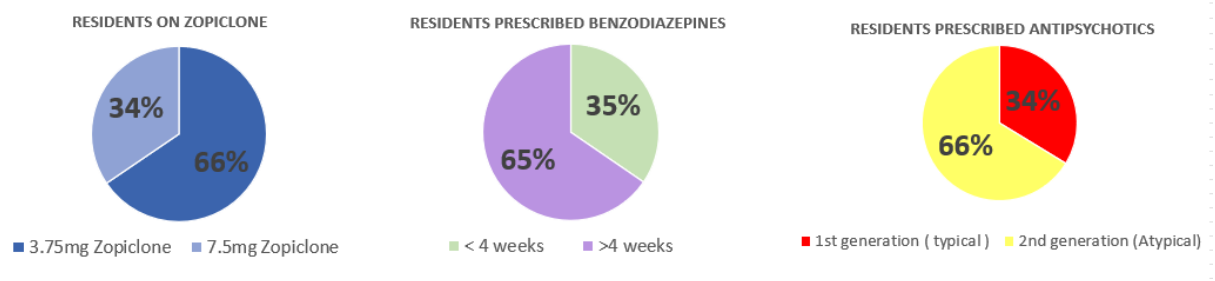

Figure 1: Common prescribing trend comparisons on Zopiclone (3.75mg recommended dose and 7.5mg),benzodiazepines (less than 4 weeks recommended and more than 4 weeks) and antipsychotics prescribing (1st generation and second generation; recommended)

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The public health concerns of novel and unlicenced benzodiazepines: An analyses of mortality data, admission data and poisoning enquiries in England and Wales

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Benzodiazepines (BZDs) was first discovered in the 1950s licenced for anxiety, sleep disorders and epilepsy and due to a low toxicity profile, they quickly replaced older generation medication, soon to become one of the most prescribed drug class in the world[1]. BZDs are now clinically indicated for severe and disabling anxiety, debilitating insomnia and epilepsy, although they come with high risk of dependence, tolerance and withdrawal, with strict guidelines for short duration[2]. This has led to an increase for other sources of misuse within BZDs[1], including novel and unlicensed BZDs (nuBZDs) found within England and Wales. This study investigates mortality data and poisoning enquiries to address public health concerns including increased risk of poisonings and death.

The mortality data (2017-2021 inclusive) was extracted from the office of national statistics (ONS) where deaths due to BZDs were mentioned on the death certificate. Poisoning enquiries (2017-2022 inclusive) were analysed via the UK poisoning database (UKPID), where the national poisons information service (NPIS) took in telephone enquires providing information on enquiry date, demographic location, age, gender, agent, circumstances, poisoning and symptom severity (MAXPSS), and comments on each enquiry. The analyses on hospital episode statistics (HES, 2017-2023 inclusive) based in England and Patient Episode Database for Wales (PEDW, 2017-2022 inclusive) based in Wales, both provide admission due to BZD poisonings.

The overall number of nuBZDs have increased from 15 deaths in 2017 to 178 deaths in 2021. Where flubromazolam and etizolam illustrating the highest increase, where it skyrockets after 2020. The number of NPIS poisoning enquiries have decreased from 9 enquiries taken in 2017 to no enquiries in 2022. 20-29 year

old were more associated with minor symptoms and no significant difference in MAXPSS between genders (t-test, P>0.05). HES shows a decrease in admission due to benzodiazepine poisonings, where a 53% reduction from 2020-2021 tax year to 2022-2023. PEDW data also shows a reduction in admissions due to benzodiazepine poisoning displaying a 41% decrease.

Where mortality rates are increasing, but admission and poisoning enquiries are decreasing for nuBZDs, there is a concern for the public health, indicating illicit use of BZDs. The Welsh Emerging Drugs and Identification of Novel Substance (WEDINOS) stated in 2022-2023 there were 1208 samples submitted for analyses that was thought to be diazepam, 308 of which were nuBZDs[3]. This tells us that data on admission and poisoning enquires may be misleading, as actual prevalence, where of the 25 samples found of nuBZDs on the UKPID, could be greatly higher.

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Establishing the correlation between benzodiazepine poisonings and prescribing patterns in the context of polydrug use: An analysis of patient demographics, outcomes and the suitability of flumazenil as an antidote

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In the United Kingdom benzodiazepines (BZDs) are prescribed for short-term treatment, categorized by half-lives as anxiolytics or hypnotics[1]. Despite the advice to limit use due to the risk of dependence and tolerance, recent studies reveal a surge in BZD misuse, notably in polydrug scenarios with opioids and alcohol[2], posing a heightened risk of fatal outcomes. The Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) service highlights BZDs as the most commonly identified psychoactive substance, often contaminated with harmful additives[3]. Flumazenil, a BZD antidote, is licensed for specific overdose situations, but its role in intentional BZD poisonings within polypharmacy remains unexplored. Concerns about potential adverse effects, including seizures and cardiac arrhythmias[4] necessitates a critical evaluation of its appropriateness. This study aims to comprehensively analyse BZD prescription patterns, mortality statistics, and clinical attributes of poisonings in England and Wales, with a focus on their association with polysubstance abuse. The findings aim to inform the potential implications for future flumazenil use in addressing these complex cases.

An analysis using three databases occurred covering England and Wales from 2017 to 2022. Data from multidrug poisoning enquiries, as reported by the National Poisons Information Service (NPIS) and documented in the United Kingdom Poisons Information Database (UKPID) were examined. An exclusion criterion was applied to filter out irrelevant cases. The focus was on assessing patient demographics, outcomes and the administration of flumazenil in these poisonings. Furthermore, BZD prescribing trends were explored using primary care data from the All Wales Therapeutics and Toxicology Centre (AWTTC). The study also incorporated information from the Office of National Statistics (ONS) to investigate mortality rates where BZDs were mentioned as a contributing factor to the fatality. This comprehensive approach aimed to provide a detailed analysis of the subject matter.

Dispensed BZD prescriptions in England and Wales have notably decreased, particularly for diazepam and loprazolam, but mortality rates involving BZDs have gradually risen over the past six years. Deaths solely attributed to BZDs remain minimal, averaging 23 individuals per year, but instances where BZDs are mentioned on death certificates combined with other substances have increased, reaching 509 deaths in 2022. The emergence of new psychoactive substances, including BZD analogues, has led to a 92% increase in fatalities from 2017 to 2022. Mortality rates among males and females varied in both countries with males in England showing a gradual annual increase. Males accounted for the majority of fatalities in both suicide and non-suicide mortalities, but females accounted for more poisoning cases which predominantly occurred intentionally, particularly among individuals aged 20-59 years. Flumazenil utilization was limited and was often contraindicated in the mixed overdose cases but a 54% positive response rate was seen in the cases where it was administered, although there was uncertainty regarding patient outcomes in all administered cases.

This study investigates the correlation between benzodiazepine (BZD) prescribing trends and mortality rates from polysubstance poisonings. Contrary to the hypothesis that increased anxiety and demand for mental health service would lead to more BZD prescriptions, a notable reduction in prescribed items for seven out of 14 licensed BZDs was observed. This unexpected decline suggests a possible shift towards deprescribing, aiming to mitigate long-term dependence and tolerance issues. However, the study's findings reveal a simultaneous increase in mortality rates associated with BZDs, potentially linked to patients seeking relief through illicit drug abuse due to limited access to mental health services. Despite a decline in NPIS enquiries, the study proposes that poisonings from prescribed BZDs might no longer necessitate professional intervention, and illicit BZD consumption could be driving specialized interventions. Flumazenil, an antidote for BZD poisoning, showed infrequent use, emphasizing the need for further research to assess its effectiveness, particularly in cases of polysubstance misuse. The study highlights the importance of healthcare providers adhering to prescribing guidelines and prioritizing patient safety in the context of prevalent mental health conditions like anxiety.

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Service User Feedback on Community Pharmacy Services: A Scoping Review

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The role of the community pharmacist has evolved greatly. Many advances have been applied to community pharmacy (CP) services available to the public. The 2019 “Pharmacy: Delivering a Healthier Wales” documents a goal of every CP having an independent prescriber by 2030 [1]. The newest pharmacy contract in April 2022, known as “The New Prescription”, emphasises the delivery of independent prescribing services (IPS) within CP.[2] Whilst the pharmacy IPS (PIPS) [3] is a relatively new concept, it is prominent and will continue to show growth, yet no widescale patient feedback questionnaire has been developed. This study aims to review the current literature available surrounding service user feedback on CP services, with the intention of informing the wider project team (WPT) on how they can obtain patient feedback effectively. They intend to launch a patient feedback survey surrounding PIPS. To aid the WPT in their development of the survey and creating a feedback strategy, there are project objectives. These include exploration of current methodologies utilised to collect service user feedback on CP services, description of the recruitment strategies, identify the common themes and type of feedback, and the type and style of questions asked.

A scoping review was undertaken to address the project aim. [4] The research title followed the PCC (population, context, and concept) framework, typically utilised to shape the title for a scoping review.[4] Inclusion and exclusion criteria were developed for the selection of peer reviewed articles. A search strategy was established by selecting appropriate keywords, some of which included “user, patient, client, satisfaction, experience, opinion, pharmacy services and UK”. Four databases were searched to identify appropriate papers (Scopus, Web of Science, Medline and Cinahl). An initial result of 239 papers were identified across the four databases, 192 papers remained once duplicates were removed. The titles and abstracts were initially independently reviewed by two people against the inclusion and exclusion criteria[4]. After this process, the full text of the remaining 28 papers (2005-present) were assessed for eligibility, independently by two reviewers.[4] Of these, a final total of 18 papers were included in the study and subsequently analysed. The relevant information was extracted and analysed by the aim, brief methodology, recruitment strategy, location, and service. The common themes were identified to summarise the main areas which were explored throughout the papers.

Out of the 18 papers, four were conducted as semi structured interviews, one was both a rapid review and qualitative study, two were systematic reviews, seven were questionnaires, one was online feedback, allowing the public to publish an account. One involved customer feedback cards, one was a two staged approach, in the form of a questionnaire and semi structured interviews, and one a mixed methods study. The common themes relating to the type of feedback identified across the papers included: accessibility to the pharmacy, privacy, relationship and interaction with the community pharmacist, communication with / the role of the community pharmacist and the extent of awareness of CP services. There were both positive and negative aspects to the type of methods in which service user feedback was collected. Accessibility to CP was arguably

the most frequently discussed topic, apparent throughout the papers, acting as either a barrier or facilitator to service users' attendance.

For future work, these findings are applicable to the WPT in how they develop their questions; the focus could be on these commonly identified themes of feedback. Online methods of collecting feedback have proven to be advantageous, however could favour certain populations thus introducing potential response bias. A mixed methods approach of paper and online feedback strategies could be advisable. Moreover, for the WPT, it is integral that efforts and considerations are made to develop a method and recruitment strategy which is suitable for all demographics and ages, to be successful for their future collection of service user feedback on PIPS.

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Cell Surface and Subcellular Analysis of HER2 in the Delivery of Tz (Herceptin) using Nanoparticles

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Breast Cancer (BC) is the leading cause of cancer deaths behind Lung Cancer worldwide and the most diagnosed cancer amongst females.[1] Approximately 20% of BC overexpress the membrane receptor Human Epidermal Growth Factor Receptor 2 (HER2) and such BCs ($HER2^+$ BC) are seen to be more aggressive and lead to a poorer patient prognosis.[2] Trastuzumab (Tz), under the brand name Herceptin, is a monoclonal antibody (MAB) that targets HER2 and has been used to treat HER2+ BC since 1998. It works in three ways: mediating an immune response, delivery of cytotoxic small molecules into the cell and by inducing receptor degradation. However, Tz is not readily internalised once bound. This is a problem because two of its three functions rely on it entering the cell. As a result, HER2 will not be degraded and thus downregulated, which may not have the desired affect on cell proliferation and survival. It has been proven that by crosslinking HER2, endocytosis is induced more readily and thus receptor degradation promoted.[3] In this study poly(lactic-co-glycolic acid) (PLGA) nanoparticles are utilised for their ability to be coated with antibodies, and the possibility of them crosslinking HER2, inducing endocytosis. This study explored, using immunofluorescence, to identify HER2 dynamics after being cross linked at the cell surface with Tz-coated nanoparticles (TzNPs).

Immunofluorescence (IF) was the labelling method in this study. Four areas were explored in both SKBR3 ($HER2^+$ BC) and MCF7 ($HER2^-$ BC) cells namely via subcellular distribution analysis of Early endosomal autoantigen 1 (EEA1), HER2 alone, HER2 after Tz treatment, and HER2 after TzNP treatment. In the TzNP experiment the cells were treated with the NPs for 10mins, 1h or 5h, with the NPs having valencies of 0 (control), 10, 30 and 50 antibodies per NP. For all experiments the cells were observed under, and images taken by a widefield and confocal microscope.

Successful labelling of EEA1 and HER2 was achieved in both cell types. In the TNP experiment, however, no significant difference in HER2 localization was observed between the different treatment times or valencies. The images showed HER2 having remained on the cell surface, endocytosis having not been induced. HER2 grouping was observed on both treatment and control cells.

Despite HER2 grouping being observed, it is confounded by its presence on the controls too, this could suggest the NPs are interacting with the cell membrane non-selectively causing the HER2 grouping effect being observed. Furthermore, next to no Tz fluorescence was observed across all cells, suggesting the NPs have been washed away in the IF process, which may have had an effect on the results. This may indicate IF being a sub-optimal labelling method in this case, and other methods (e.g. immunohistochemistry) could be explored. The main limitation of this study is that, due to time constraints, no repeats were done for the TNP experiment. Furthermore, when coating the NPs with Tz, it cannot be controlled or measured what part of the antibody binds to the NP. This means that the Fab (antigen binding) part of Tz may not be exposed for HER2 binding, thus making that some Tz antibodies on the TNP could be useless, potentially affecting its intended effect of

grouping HER2, inducing endocytosis. There is also the question of the efficacy of the antibodies used; cross-reactivity (binding to similar targets) and non-specific binding (binding to other cellular components) are always challenges with IF, and are difficult to overcome. In conclusion, there has been a successful production of a HER2 labelling method post TNP administration with evidence of HER2 grouping at the cell surface; however, this is confounded by HER2 grouping in the controls. Near negligible evidence of TNP-induced HER2 endocytosis further indicates limitations in the methodology. Further research would be necessary to draw concrete conclusions, such as, increase in treatment time to 7h, as evidence suggests endocytosis can take 5-7h,[4] and an exploration of other labelling techniques and the effects they have on the NPs being used.

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A retrospective study to quantify and evaluate prescriber adherence to new intravenous iron guidelines for dialysis dependent patients in Cardiff North Renal Unit

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End-stage chronic kidney disease (CKD) patients require haemodialysis as the kidneys fail to remove metabolic waste due to progressive kidney scarring affecting function. Patients receiving haemodialysis treatment have a high prevalence of iron-deficiency anaemia caused by increased blood loss and reduced iron absorption. Therefore, intravenous (IV) iron dosing is required to limit comorbidities and improve quality of life impaired by iron-deficiency anaemia. Previous IV iron dosing guidelines recommended a reactive iron dosing regimen to anaemia, but a 2019 randomised control trial "PIVOTAL" reported improved patient iron blood results with a proactive regimen[1,2]. This trial also demonstrated proactive dosing reduced the need for erythropoiesis-stimulating agents, which are used to make red blood cells[2]. Erythropoiesis-stimulating agents are associated with increased risk of thrombotic events, so this reduced dose required improves patient safety. IV iron dosing guidelines for patients receiving haemodialysis changed accordingly for haemodialysis units in Southeast Wales by the Cardiff and Vale University Health Board[3]. However, University Hospital Wales dialysis inpatients blood results remained indicative of iron-deficiency anaemia and iron-overloading. Hence, this study is auditing clinical data from Cardiff North Renal Unit for conformity with the new proactive iron-dosing guidelines and evaluate causal links. Principally, this study aims to direct future research so poor iron outcomes and consequent events are reduced for patients on haemodialysis[3].

Anonymised patient iron haematinics data (transferrin saturation, ferritin and haemoglobin levels) from Vital Data Renal E-prescribing Software from Cardiff North Renal Unit for 201 patients were retrospectively assessed against new guidelines for IV iron dosing for a seven-month period, April to October 2023, to quantify prescriber adherence[3]. In-practice service reviews investigated reasoning behind practitioner prescribing to detail further reasoning and enhance comprehension on quantified guideline adherence.

189 patients resulted in 1,041 monthly reviews that were assessed for adherence out of a potential 1,323. Not all months were assessed due to missing patient data. Prescriber adherence followed IV iron prescribing guidelines for a total of 585 (56%) out of 1,041 reviewed months, while for 456 (44%) months the prescriber was not within guidelines. Out of the 456 patient months the most common cause for a non-adherent prescribing was required iron doses not being prescribed, occurring for 165 patient months. Additionally, 136 instances of underdosing, 75 instances of unrequired prescribed doses, 66 instances of doses prescribed too high and 6 double prescription errors were recorded. Of these, 133 were non-adherent for only one month at a time comparative to 323 months were non-adherent for consecutive months at a time.

Results of prescribing based on patient iron haematinics to new IV iron dosing guidelines in Cardiff North Renal Unit shows low prescriber adherence resulting in both iron overloading and iron-deficiency anaemia, affecting.

Old IV iron sources resulted in high rates of anaphylaxis may have created stigma influencing prescriber decisions[4]. Additionally, lack of prescriber knowledge for these specific guidelines could be considered rationale behind non-adherence. In-service reviews suggested additional reasoning for low adherence rates included the prescriber focusing on haemoglobin levels predominantly over ferritin and transferrin saturation when decision making and accidental double prescriptions. Consequences of low prescriber adherence rates to guidelines affect patients negatively by increasing patient risk to co-morbidities such as stroke and reduces patient quality of life[2]; therefore, it is necessary to improve prescriber adherence to dosing guidelines through further education, so patients realise the full benefits of treatment.

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An analysis investigating the provision of licensed benzodiazepines, along with toxicity and multi-agent poisonings in England and Wales

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Drug overdoses are frequently observed with benzodiazepines either as single- or multi-drug intoxication. Single-drug intoxication with benzodiazepines often result in unconsciousness, however, these are not usually fatal and display low mortality rates[1]. On the other hand, benzodiazepines involved in multi-drug poisonings with other drugs or ethanol result in a more severe prognosis with many accounts of fatalities[1]. Certain interactions with benzodiazepines are well known as they can exacerbate their CNS depressive effects which could be fatal such as alcohol and opioids[2]. Concerns regarding the prescribing, illicit and non-medical use of benzodiazepines are on the increase. This study aims to explore the trends in the dispensing of licensed benzodiazepines and the correlations between benzodiazepines and multi-agent toxicity.

Three datasets were analysed providing data for England and Wales between January 2017 and December 2022. All Wales Therapeutics and Toxicology Centre (AWTTC) provided the primary care dispensing data. The dispensing trends of licensed benzodiazepines in primary care were explored, where items dispensed was assessed. Mortality data including the mentioning of benzodiazepines on death certificates were supplied by the Office for National Statics (ONS). A breakdown of the licensed benzodiazepines mentioned on death certificates were also provided along with a breakdown of multi-agent toxicity data including cases of benzodiazepines taken in conjunction with alcohol resulting in mortality. Benzodiazepine poisoning enquiry data was supplied by the National Poisons Information Service (NPIS) where data was derived from the United Kingdom Poisonings Information Database (UKPID). From all data sets diazepam and novel benzodiazepines were excluded due to the parallel studies being conducted.

A general decrease in the dispensing of benzodiazepines in primary care between 2017 and 2022 can be seen, although three benzodiazepines clobazam, clonazepam and midazolam, show an increase. Despite this, mortality rates are on the incline with a 37.6% mean increase of cases where deaths related to benzodiazepine poisonings recorded on death certificates between the years 2017 to 2021. With regards to multi or single agent prevalence on death certificates, 94.9% of these deaths were taken with other drugs The number of enquiries made to the NPIS regarding benzodiazepines has remained reasonably constant regardless of the deceasing dispensing trends. The most common enquires concerning lorazepam, clonazepam, alprazolam and temazepam. Intentional poisonings accounted for almost half of all enquiries regarding licensed benzodiazepine poisonings (excluding diazepam), recreational abuse accounted for 10% of enquiries, with alprazolam constituting 83% of these enquiries. In terms of the severity of the enquiries, 78% of enquires with a MAX PSS regarded as severe were multi-agent poisoning enquiries. 31.7 % of the severe enquiries were co-ingested with either alcohol, opioids, or both.

Although prescribing of many benzodiazepines are decreasing, mortality and poisoning enquiries have shown an increase suggesting increased use of illicit benzodiazepines. Possible illicit use surrounding alprazolam is of particular concern with it accounting for majority of reactional abuse enquires. Alprazolam is only available

on private prescription, nevertheless it was the most mentioned licenced benzodiazepine on death certificates. Alprazolam as well as other benzodiazepine are often taken alongside other medications[3]. An analysis of the data has displayed that multi-agent poisoning is resulting in a higher severity of toxicity and mortality rates over the years. With frequent reports of intentional or recreational abuse, mental health, and the access of benzodiazepines illicitly are of concern.

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Exploring Challenges and Opportunities in Community Pharmacies: An Analysis of Nutritional Care Practices, Attitudes and Educational Needs

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Malnutrition is a pervasive public health issue that is commonly overlooked and undertreated. Projections indicate that one-half of the global population will be affected by malnutrition by 2025. As the prevalence of malnutrition continues to rise, there is a pressing need to expand access to nutritional care[1]. Community pharmacists are well-positioned to implement such public health initiatives due to their accessibilit[2]. However, there is limited research exploring nutrition practices among community pharmacists, with none conducted specifically in Wales. In light of this, this analysis aims to evaluate the experiences of community pharmacists serving Wales in providing nutrition services and identify the obstacles they face in providing such care in order to improve nutritional care practices.

The study adopted a descriptive qualitative approach to explore community pharmacists' experiences delivering nutritional care. English-speaking community pharmacists serving Wales were eligible to participate in the study. A purposive sample of five community pharmacists was recruited via e-mail. Data were collected through semi-structured, individual interviews and analysed using a deductive thematic analysis approach. Interviews were recorded and transcribed verbatim[3]. Interview transcripts were pseudonymised, and audio recordings were deleted post-transcription.

Most Welsh community pharmacists were satisfied with their nutritional care practices and considered it their professional responsibility. However, several barriers to effective nutrition care have been identified, including a lack of interprofessional collaboration between dietitians and community pharmacists, inadequate nutrition training, competing priorities and limited demand for broader nutritional services. Implementing direct referral pathways between community pharmacists and dietitians, improving the quality of nutrition education, nurturing commitment to public health and increasing public awareness of the range of nutrition services provided in community pharmacies were recommended by participants to address these challenges. Nutritional care practices and learning appear to be influenced by the level of demand and interest in this field.

Community pharmacists show a positive appreciation and attitude towards nutritional care. However, it is often poorly integrated into daily practices. The study's findings suggest the need for targeted interventions to optimise nutritional care. Further research is needed to assess the practicality and impact of the recommended interventions. Overall, a more concentrated effort is required to plan and improve community-based nutritional services to maximise their impact on wider public health.

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Characterisation of disc-shaped cryogels with negatively charged moieties for use as a biomaterial scaffold to deliver demyelinating agents to brain slice cultures

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Multiple sclerosis (MS) is an autoimmune condition whereby immune attack of neuronal axons results in areas of demyelination1. An accurate ex-vivo model of MS is foundational to the development of pro-remyelinating and neuroprotective therapies. However, this is currently represented with global demyelination of entire slice cultures2. Eigel et al have demonstrated successful demyelination of grey matter in human foetal brain slices by placing cryogels – a novel biomaterial developed from hydrogels formed under freezing conditions – adjacent to slices in culture. Charge-neutral cryogels were found to adhere to the tissues and cause damage on removal whereas this was not observed with negatively charged cryogels, theoretically due to the similar negative charges generating sufficient repulsion between the cryogel and the tissue membrane to prevent growth into the cryogel scaffolding3. This report aims to characterise some of the physical properties of disc-shaped, negatively charged PEGDA-co-SPA cryogels for researchers to use on top of neural slice cultures when modelling focal demyelination in otherwise healthy tissue.

We synthesised disc-shaped 50% SPA cryogels of 1, 2, 3, and 4mm diameter and 3mm cryogels at 0%, 50%, and 95% SPA. Cryogels were analysed for successful cross-linking via FTIR analysis and swelling measured via microscopy and calliper gauge analyses. Swelling analyses were conducted on the 50% SPA cryogels at various diameters to identify a swelling ratio between the dried and hydrated cryogels. Loading and retention analyses were conducted using the charged dyes Eosin Y (negative), BODIPY (zwitterionic), and DiI (positive) to identify the effect of negatively charged cryogels on their uptake and release onto cell culture slices. Finally, compression testing was conducted using an indenter to quantify the structural integrity of the formed cryogels.

FTIR analyses of cryogels formed under 30 seconds and 2 minutes UV exposure indicated that 30 seconds is sufficient for complete cross-linking between the monomers. Unexpectedly, we found slight variation between the swelling ratios of differently sized cryogels, ranging from 1.3 to 1.7x larger when hydrated compared to the dried state. This was likely due to natural shape changes in the cryogel upon drying meaning the diameter was no longer consistent around the circumference of the gel. A Young's Modulus of approximately 3.67kPa was obtained from compression testing. Loading and release analyses indicated that there was no specific loading of BODIPY onto the cryogels but some additional loading of DiI to the cryogel scaffolding indicates the potential for electrostatic interactions between the cryogel and a loaded dye. Release studies showed minimal penetration of the dyes through a millicell cell culture insert, positively suggesting regional constraint of the applied solution and the potential for more localised drug delivery to cell slice cultures.

Cryogels have a promising future in the drug delivery field due to their ease of manufacture, adaptability, and largely advantageous physical properties. Their robust nature allows them to be easily handled yet their softness also enables use on tissues as delicate as neural slices. We provide some insight from our experiments into the characteristics of negative PEGDA-co-SPA cryogels and how changes in 3-Sulfopropyl-Acrylate (SPA) content affects these. Ultimately, the next steps are for testing to occur with LPC loaded cryogels to investigate their loading and release characteristics on tissue samples, but we offer here a fundamental base from which further research can follow.

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An investigation into the prevalence of prescribing medicines associated with harm in care homes throughout Wales in 2015

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Older adults in care homes are particularly susceptible to medicines harm. There are several reasons for this; one being that they are more likely to be taking a greater number of medications to treat multiple co-morbidities. This can lead to polypharmacy, whereby five or more medications are prescribed to an individual patient. A

study by Shah et al[1] has found that there is limited monitoring of the prescribing which occurs within care homes. As well as this, older adults are more likely to have reduced liver and/or kidney function. Together, these factors can increase the risk of adverse events, drug interactions and subsequent harm. Specifically, this study aims to identify potentially inappropriate prescribing and administration of antibiotics for urinary tract infections (UTI) as well as the prescribing of drug combinations known to increase the risk of acute kidney injuries (AKI). Medications with anticholinergic burden (ACB) scores will also be considered because of the side effects associated with them.

Data from 12 care homes in the UK listed the drugs prescribed and administered to 329 residents between February and October of 2015. The data was analysed using descriptive statistics. This involved identifying drugs of interest based on guidelines such as those from the National Institute for Health and Care Excellence (NICE). Namely, trimethoprim and nitrofurantoin with a dose indicating treatment for UTI, drugs with an anticholinergic burden score from the All Wales Prescribing Indicators[2] and medications found to be most commonly associated with patients hospitalised with acute kidney injuries[3].

On average, eight medications were prescribed to each resident, indicating prevalent polypharmacy. Every resident was prescribed at least one medication which ranged to a maximum of 24 medications being prescribed to an individual resident. In total, 66 antibiotics courses were prescribed to 58 residents to treat UTI both acutely and prophylactically. Only 33.3% of these courses were considered appropriate in terms of treatment length prescribed (three days for lower UTI in females and seven days for males). 14 courses were established to be too long, and 30 courses considered to be too short. When analysing the administration of the antibiotics, it was found that 77.3% courses involved at least one missed dose with 15 courses not being administered at all. When analysing prescribing around AKI, 81% of residents were not prescribed any combination of drugs that may increase the risk of AKI. This meant that 55 residents were prescribed some sort of combination i.e. more than two drugs, that can increase their risk of an AKI. This ranged from 36 residents prescribed two implicated drugs to two residents being prescribed a total of five implicated drugs. For anticholinergic burden, 19% of residents analysed had a clinically relevant ACB score (2 or greater). This ranged from 29 residents having a score of two to one resident having a total score of five. The remaining 81% of residents had an ACB score under one which indicates their risk is minimised.

The antibiotic aspect of the investigation is particularly concerning given that poorly treated urinary tract infections can lead to confusion, delirium and falls in older adults[4]. Although the prescribing around AKI and anticholinergic burden was more positive, several residents were still prescribed inappropriately. Older adults are more at risk of an AKI due to age-related factors like impaired renal function. It has been found that a history of AKI is associated with increased risk of chronic kidney disease in older people which can greatly impact on quality of life[5]. Anticholinergic drugs can cause delirium, confusion and cognitive impairment. Therefore, it is no surprise that Wong et al[6] found that anticholinergic burden was strongly associated with increased risk of falls and hospitalisation in adults aged over 65. On the whole, increased monitoring of the quality of prescribing and administration of medications in care homes is needed. This may be achieved by introducing a multi-disciplinary team into care homes. For example, Stuijt et al[7] found that drug-related problems in care homes were reduced following the introduction of pharmacist-led medication reviews. Overall, the data gathered in this investigation should aid in updating guidelines used by prescribers to reduce the risk of potential harm in an already vulnerable patient demographic.

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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:

Analysing the Interaction between the Immune Complement Protein C3 and its Cleavage Products C3b, iC3b with the Blood Coagulation Protein Thrombin

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A Secondary Data Analysis of Independent Prescribing Service consultations in Wales 2020-2022

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Evaluation of Pharmacist involvement in a TIA Outpatient Clinic: Working within a Multi-Disciplinary Team and Adherence to National Guidelines

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Tackling the Dual Challenge: Diabetes and Prosthetic Joint Infections in Knee Replacement Surgeries: A rapid review

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Are the indentation properties of commercially available Simulab® and Ecoflex™ Gels suitable for inclusion in a puncture performance test for Microneedle Array Patch (MAP) products?

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Complement proteins in the pathogenesis of first-episode psychosis and Schizophrenia

Erin Howells and M Heurich-Sevcenco
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A rapid review of anaemia as a risk factor for prosthetic joint infections after a primary total joint replacement

Amy Hubbard and P Prokopovich
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Identifying and characterising a synthetic surrogate of human skin to be used in a puncture performance test for Microneedle Array Patch (MAP) products

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Evaluation of Independent Prescribing in Community Pharmacies Across Wales with a Focus on UTIs, June 2020 to September 2022

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Quantifying the sequence and structure homology of complement and coagulation serine proteases

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A rapid review investigating if Connective Tissue Growth Factor (CTGF) contributes to treatment failure in breast cancer

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Describing out of contract consultations delivered via the Pharmacist Independent Prescribing Service between June 2020-September 2022

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The factors influencing microneedle embedding performance in ex vivo porcine tissue

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A pharmacist's involvement in a TIA clinic; the views of service users and service providers

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Preoperative opioid use as a risk factor for developing prosthetic joint infection after total joint replacement surgery

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Rapid Review: Obesity as a risk factor for Prosthetic Joint Infection following joint arthroplasty

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Correlation Between the Blood Biomarkers of the Immune-Complement System and Cognitive Impairment in Psychotic Disorders

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PhD Abstracts

Acute arterial hypoxaemia and its impact on drug pharmacokinetics in humans; clinical and in-vitro investigation

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Arterial hypoxaemia ultimately leads to the formation of systemic and localised free radicals, activating pathways of oxidative-inflammatory-nitrosative stress. The physiological adjustments, encompassing redox and haemodynamic responses, have the potential to influence the pharmacokinetics (PK) and pharmacodynamics (PD) of both acutely and chronically administered medications. Sildenafil, a drug that acts through phosphodiesterase-5 inhibition and is clinically used for pulmonary hypertension, also serves as a short-term treatment to prevent or mitigate altitude-induced pulmonary vasoconstriction, a key factor in the development of high-altitude pulmonary oedema (HAPE). This thesis aims to simulate the PK/PD outcomes of sildenafil under acute hypoxaemia and identify the underlying mechanistic pathway that drives PK/PD alterations under hypoxia. The PK/PD profile of a single oral 100 mg sildenafil oral tablet was simulated using R V.3.6.3 with the IQRtools package. A Monte Carlo method was employed, involving 1000 subjects, with a one-compartment first-order elimination and absorption model. The HepaRG cell line served as an in-vitro model to predict the intrinsic clearance (Clint) of sildenafil under hypoxia (1% O2). This was accomplished by evaluating CYP3A4 and CYP2C9 turnover activities and investigating the associated mechanistic pathway. Hypoxia resulted in a significant decrease in the turnover activity of both CYP3A4 and CYP2C9, leading to a 29% reduction in Clint compared to the normoxic control. Monte Carlo simulations revealed that acute hypoxia increased the maximum concentration (Cmax), half-life (t1/2), area under the curve (AUC 0-∞), as well as AUC above the inhibitory concentration 50% (IC50). Hypoxia stimulated stressors such as cytokine and superoxide production, had exerting a negative regulatory effect on CYP3A4/2C9. The preservation of CYP3A4/2C9 activity under hypoxia was achieved by employing reactive oxygen species (ROS) scavengers like Tiron. Furthermore, hypoxia may regulate CYP3A4/2C9 through the modulation of the pregnane x receptor (PXR). The MAPK/ERK signalling pathway appears to be the target pathway for this regulation. In conclusion, hypoxia has the capacity to alter the PK/PD profile of drugs, warranting dosage regimen adjustments, particularly for drugs with narrow therapeutic indices. Further mechanistic studies focusing on the PXR pathway are necessary to fully comprehend the mechanisms underlying hypoxia-induced alterations.

Targeting Mycobacterium tuberculosis: Design and synthesis of CYP121A1 inhibitors

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Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (Mtb), which continues to be a highly lethal disease owing to the drug resistance crisis. Drug-resistant strains of Mtb represent a major therapeutic challenge, so new anti-tuberculosis agents are desperately needed. Among 20 Mtb cytochrome P450 enzymes, CYP121A1 was found to be a target of interest owing to its importance for Mtb cell viability and its high affinity to azole antifungal drugs. The aim of this project was to design and develop novel CYP121A1 inhibitors for treatment of TB with both optimum binding and antimycobacterial activity. In the present work, docking studies using MOE and MD simulations using the Desmond programme of Schrödinger software were used in designing different series of potential CYP121A1 inhibitors that mimicked the binding pattern of the CYP121A1 natural substrate, the cyclodipeptide dicyclotyrosine (cYY). Different scaffolds were used in the design: diaryl pyrazoles (Chapter 2), benzoxazoles (Chapter 3), chroman-4-ones (Chapter 4) and tetralones (Chapter 5), and various potential haem binding groups were incorporated including imidazole, triazole, tetrazole and pyridine. The designed ligand structures showed a consistent binding mode in a region of the active site located between the haem iron and the expected access channel, between the F and G α-helices, in a position comparable with cYY in CYP121A1. A synthetic scheme for each series was developed after several optimisation trials. Final products were obtained with varying yields followed by structural characterisation using NMR (1H, 19F and 13C) along with purity analysis using HPLC-MS and/or elemental analysis. All final compounds were evaluated against Mtb H37Rv (MIC90) and compared with the reference compounds: rifampicin, isoniazid, and kanamycin. The most promising series were screened against resistant

Mtb strains. CYP121A1 binding affinity studies (KD) were performed using UV-Vis spectral absorption and compared with cYY. Protein-detected 1D 19F NMR spectroscopy was conducted as an additional binding test and cYY was used as a reference standard. The chroman-4-one and tetralone series were the most promising scaffolds followed by the pyrazole series, whereas the benzoxazole series was inactive. This research led to an effective design and synthesis of CYP121A1 inhibitors, which demonstrated good antimycobacterial activity against Mtb susceptible and resistant strains with optimal binding affinity.

Biochemical investigation of zinc transporters to discover their functional mechanism in cells

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Zinc is one of the most abundant micronutrients in the human body and it plays a vital role in many normal cellular processes. The cellular zinc level is tightly controlled by zinc transporters, including the ZIP family, which function to increase cytosolic zinc levels. The alteration of this function has been associated with human diseases, including cancer. ZIP7 belongs to the ZIP family of zinc transporters and resides on the endoplasmic reticulum store. It is responsible for releasing zinc from stores after it has been phosphorylated by CK2 on residues S275 and S276. This ZIP7-mediated zinc release inhibits tyrosine phosphatases and activates cellular tyrosine kinases, several of which are associated with progression of cancer. Moreover, two other ZIP transporters, namely ZIP6 and ZIP10, have been demonstrated to be involved in cell growth and proliferation by importing zinc across biological membranes to cause cell rounding and detachment, essential for migration and the first step of mitosis. In order to achieve this, the N-terminus of ZIP6 has to be cleaved before these transporters relocate to the plasma membrane. The present study generated novel constructs to understand the functional mechanisms of these transporters. Firstly, the activation of ZIP7 was investigated by mutating all four residues S275, S276, S293 and T294 predicted to be phosphorylated. This study found that all four of these residues were required for ZIP7 maximal activation. Secondly, the role of N-terminal cleavage of ZIP6 and ZIP10 was investigated by making chimera constructs replacing the usually cleaved N-terminus with the ZIP7 N-terminus, known not to be cleaved. This study found that the N-terminal cleavage of ZIP6 and ZIP10 was required to enable the cells to round up and detach, indicating a critical role for the N-terminus of ZIP6 and ZIP10 in this mechanism. These findings not only help us to understand the mechanism for these transporters but also enable new tools to be discovered for diseases, such as cancer, that are exacerbated by these transporters.

Impact of photodynamic therapy on different breast cancer subtypes in-vitro

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Photodynamic Therapy (PDT) is a novel therapeutic strategy. It is a type of phototherapy that involves activating an administered drug/chemical in the body with a specific wavelength of visible light to promote tumour cell death. Breast cancer (BC) is the leading cause of mortality in women globally. Indeed, while many luminal A patients have a better prognosis, some sub-types of the disease, such as triple negative, luminal B and HER2+ BC's, are inherently more aggressive conferring poorer prognosis. Furthermore, many patients acquire resistance to current treatments resulting in disease recurrence and metastasis. PDT is a promising breast cancer (BC) treatment being explored in neoadjuvant, intraoperative, and recurrence settings, however responses are heterogeneous between patients. Deciphering this heterogeneity is required to understand how best to use PDT. The aim of this in-vitro project is to explore whether PDT sensitivity relates to the intrinsic phenotype of BC and to determine the underpinning response mechanism. An in-vitro PDT methodology was developed and optimized for use in various breast cancer cell lines, along with uptake, dark toxicity and phototoxicity studies. Open-access transcriptome analysis was conducted to identify potential PDT-response and PDT-resistant gene-sets/pathways. Consequently, the associated mechanistic changes that underpin PDT anti-tumour impact were further explored.

Risk factors in prosthetic hip/knee joint replacement infections incidence and patient outcomes

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Periprosthetic joint infection (PJI) is a severe complication following total joint arthroplasty which is associated with mortality and morbidity risks. Perioperative identification of modifiable and not modifiable PJI risk factors is essential for educating patients on their risks of complication and improving surgical decision-making. Aims: 1. Examining the association between uncertain variables of smoking, intraarticular steroid injection, anticoagulants and fixation types, and risk of PJI in hip arthroplasty. 2. Identifying risk factors of PJI in total hip and knee joint replacement surgery in the UK. Methods: • Systematic review and meta-analysis. Systematic search conducted through MEDLINE, EMBASE, CINAHL and Cochrane databases. Odds ratio (OR) with 95% confidence interval (CI) using random effect models utilised. • Conducting a retrospective observational study involving 91,038 hip or knee joint replacements performed between 2007-2019 in England and Wales. Investigating the association between PJI risk and patient characteristics, medical and treatment histories, and surgery characteristics using Cox proportional hazards. Data obtained from Clinical Practice Research Datalink linked to Hospital Episode Statistics data. Results: • Overall OR to develop PJI for steroid injection is 2.12 (95% CI 0.58-7.72, $p = 0.250$); smoking is 1.54 (95% CI 1.25-1.91, $p < 0.05$). The systematic search found no association between anticoagulants and PJI risk, while it was difficult to draw conclusions regarding fixation method due to inconsistencies in the literature. • For THA, DM, active cancer, hypertension, using NSAIDs and DMARDs < 3 months were risk factors for PJI. Male gender, BMI 25-30 kg/m2, DM, active cancer, using NSAIDs < 3 months were risk factors for PJI following TKA. Conclusion: This study's findings provide information that allows healthcare providers to develop and incorporate preventative strategies for PJI for patients undergoing TKA/THA in clinical practice.

Regulatory convergence or harmonisation? Exploring regional approaches for streamlining chemistry manufacturing and control variations and its application in Latin America compared to initiatives in Southeast Asia

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Post-approval chemistry, manufacturing and control changes (PACs) are essential in the lifecycle of a medicinal product in improving quality and maintaining supply. In recent years, the focus of harmonisation or convergence initiatives are beginning to shift to PACs due to the divergent regulations between different National Regulatory Authorities (NRAs) and the resulting complexity it brings to maintaining quality and supply. The benefits of streamlining PAC requirements and regulations across regions, for industry, NRAs and ultimately patients is widely accepted. The aims of this research were threefold. The first was to explore and assess the effectiveness of harmonisation of PACs among three ASEAN markets, namely Malaysia, Singapore and Thailand. Secondly, the research aimed to assess whether streamlining of PACs was a priority in six Latin America markets (LATAM), namely Argentina, Brazil, Chile, Colombia, Cuba and Mexico; and to ascertain whether streamlining was occurring through 'harmonisation within the region' or 'convergence to international guidelines'. Lastly, the research compared the ASEAN harmonisation initiative with the LATAM experience to determine any areas of strength from ASEAN which could be applied to LATAM. A qualitative case study approach including a systematic review, online questionnaires, group and individual interviews was adopted to achieve the research objectives. The perspectives of the Regulatory Affairs Professionals stakeholder group and harmonisation network was obtained by individual interviews. In parallel, perspectives of one LATAM industry association was obtained via group interview. An online questionnaire was complete by personnel with LATAM NRA working experience and followed up with either an online or email interview. The ASEAN interviews showed that the main motivations for harmonised requirements were trade, security and a unified mindset. However, despite their harmonisation initiatives, challenges remained for effective implementation which led some participants to believe that convergence was a better process to associate with the streamlining initiatives in ASEAN. The LATAM interviews and questionnaires exposed the low priority the

region had for streamlining chemistry, manufacturing and control (CMC) requirements. The results also confirmed that convergence through reliance was the best model to describe streamlining efforts across the region, in spite of various challenges. Harmonisation could possibly occur across the region as each market converges to international guidelines, however, this may take a long time due to challenges such as political rivalry and lack of a unified mindset. The comparison between ASEAN and LATAM showed similar challenges across the two regions which could be an indication of regions which have markets with varying degrees of disparity in regulatory capacity and expertise. The LATAM region, however, has much to learn from ASEAN's united goal of leverage across markets to support becoming an economic bloc plus the desire for patients to have access to quality and innovative medicines.

New strategies to support cell survival post- transplantation for the treatment of Parkinson's Disease

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Cell therapies hold the potential to significantly reduce the debilitating effect of several neurodegenerative diseases, including Parkinson's Disease (PD). Despite showing promise, one of the primary drawbacks is cell death after transplantation. This work aimed to explore new approaches using biomaterial-based systems to support the survival of transplanted cells after transplantation. One class of biomaterials called cryogels has been shown to possess several distinct advantages over conventional biomaterials. They are characterized by interconnected macroporous networks that not only allow fluid transport throughout their structure but also create a high surface area to volume ratio for cell growth or protein loading. In this work, the cryogels were synthesized from synthetic monomers containing poly (ethylene glycol) diacrylate (PEGDA) and either 3-sulfopropyl acrylate (SPA) or 2- (dimethylamino)ethyl methacrylate (DMAEMA), which introduced a negative and positive charge into cryogels network, respectively. Cryogel microcarriers were successfully developed using microfluidic devices to generate water-in-oil emulsion (as a template) followed by the cryogelation process. Firstly, SPA cryogel microcarriers aimed to control the release of growth factors (GDNF and BDNF), which play an important role in regulating the growth and survival of neurons, through electrostatic interactions. GDNF and BDNF showed different loading percentages into cryogels with different release profiles depending on the SPA (negative charge) amount. Moreover, biological studies confirmed the biocompatibility of cryogels and their ability to deliver GDNF and BDNF into the healthy rat brain. Secondly, DMAEMA cryogel microcarriers were utilized as another approach to improve the transplanted cells viability. This system can act as a scaffold to allow cell adhesion/ maturation and protect them during the transplantation process. The cryogelation protocol was adjusted with different freezing regimes to produce a large macroporous structure. The in vitro results showed encouraging outcomes in which neurons were able to attach to the microcarriers and develop mature and three-dimensional neuronal morphologies. Although SH-SY5Y cells (a model dopamine neuron) were able to adhere, they were unable to proliferate and differentiate, meaning further work is needed for better cell growth. Finally, we suppose that these approaches could develop into potential supportive ways of tackling cell death issues posttransplantation and that they could lead to better knowledge and later, new cell therapy approaches for the treatment of PD.

Screening honey for antibacterial activity against acinetobacter baumannii

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Acinetobacter baumannii is a frequent cause of infections in hospitals around the world which are difficult to treat due to there inherent antibiotic resistance. It is particularly prevalent in intensive care units (ICUs) and around 19.5% of A. baumannii infections in the UK resulted in bacteraemia (mostly in infants and the elderly) in 2020. Due to the challenge in treating infections caused by this bacteria, there is considerable interest in exploring natural products for compounds with novel antimicrobial activity. Honey has been used for many centuries in traditional medicines to treat infections. In addition to its antibacterial activity honey possesses anti-oxidant and anti-inflammatory properties. The aim of this project is to screen our collection of 277 honey

samples collected from across Wales for the presence of antibacterial compounds with activity against clinical isolates of A. baumannii with a particular focus on isolates resistant to multiple antibiotics. A total of 46 clinical isolates provided by Public Health Wales were characterised using a combination of phenotypic (biochemical, antibiotic and honey sensitivity testing) and genotypic (BlaOXA-51) methods. Using these approaches 35 isolates were identified as A. baumannii. Of this total 12 isolates were resistant to all of the antibiotics (Imipenem, Meropenem, Ciprofloxacin, Levofloxacin, Amikacin, Gentamicin, Netilmicin, Tobramycin) commonly used in hospitals to treat infections caused by this organism while a further 10 isolates were resistant to at least 3 of those antibiotics. To further characterise these isolates they were screened for the presence of additional A. baumannii specific genetic markers (BlaOXA-23 and Class 1 integrase (Int1)). Four different genotypes were identified: BlaOXA-51 positive22 (62.8%), BlaOXA-51 and BlaOXA-23 positive 11 (31.4%), BlaOXA-51, BlaOXA-23 and Int1 positive 1 (2.9%) and BlaOXA-51 and Int1 positive 1 (2.9%). To provide a group of A. baumannii isolates representative of the diversity of the species and which included antibiotic resistant and sensitive examples we assembled a panel of two control organisms and six clinical isolates. The 277 honey samples in our collection were first screened for antimicrobial activity against our control organisms, A. baumannii ATCC 19568 (antibiotic sensitive), OXA-23 clone 1 and OXA-23 clone 2 (antibiotic resistant isolates) using an agar well diffusion assay. Interestingly, we saw significant difference in the honey sensitivity of the antibiotic sensitive and resistant isolates. The 15 most active honey samples identified from this screen were selected for activity testing against our panel of genetically diverse, antibiotic resistant isolates of A. baumannii.

Understanding the risk of emerging bacterial resistance from the use of sore throat over-the-counter topical antibiotics

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Within Europe, antibiotics are available in over-the-counter (OTC) topical sore throat medications. As sore throats are mainly of viral aetiology, antibiotics in these medications is poor antimicrobial stewardship. It is unknown what role OTC antibiotics (bacitracin, gramicidin, neomycin and tyrothricin) play in antimicrobial resistance. This study aims to understand whether the use of OTC antibiotics could contribute to resistance development in bacteria. OTC antibiotics at during-use concentrations were tested against a panel of bacteria and mainly Gram-negative bacteria could resist their effects, with the exception of neomycin. After OTC exposure, clinical cross-resistance was gained to beta-lactam antibiotics (including ampicillin, cefotaxime, aztreonam and imipenem) and gentamicin and this resistance was mainly stable. Phenotypic and genotypic changes after OTC antibiotic exposure were assessed and many changes occurred including, increased beta-lactamase activity, increased efflux activity, morphological changes, metabolic changes and mutation in membrane protein genes. It is thought that the increase in beta-lactamase activity is due to induction of AmpC, which is predominantly responsible for the clinical cross-resistance to the beta-lactam antibiotics. Co-exposure assays were done to evaluate the impact OTC antibiotics have on aminoglycoside efficacy. It was found that gramicidin and tyrothricin both impacted the efficacy of aminoglycoside treatment, although bacitracin did not. The study concluded that gramicidin and tyrothricin depolarize the cell membrane by potassium leakage, inhibiting aminoglycoside uptake into the cell. Along with experimental lab work, a survey was constructed to understand OTC antibiotic usage. It also sought to understand how sore throat is managed, and the knowledge of pharmacists on OTC antibiotic-containing products. Although the survey has not yet been distributed, responses from pretesting indicate that some pharmacists are unaware of OTC antibiotic-containing products. This study highlights the development of clinical cross-resistance from exposure to OTC antibiotics, and therefore should not be used for sore throat products for patients seeking symptomatic relief.
