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FOREWORD

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

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

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

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

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

Rhys Thomas, Dean Routledge & Justine Jenkins
August 2021

Investigation of Structure-based drug design on the development of anticancer compounds: A Rapid Review

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Structure-based drug design is one of the computer aided drug design techniques used in the discovery and development of anticancer therapies.[1] The demand for new anticancer therapies is high as cancer is one of the leading causes of death worldwide.[2] This rapid review aims to use research from publications between 2000-2020 to determine the role of SBDD in the design and development of anticancer therapy and whether its use has a major impact on developing anticancer therapies faster and more effective.

Three databases were used PubMed, Embase and Web of Science to obtain literature evidence of the impact of SBDD through computational and in vitro and/or in vivo data. The studies were screened for the eligibility which was dependent on the inclusion and exclusion criteria. The relevant studies were read to check if they fit the inclusion criteria and were subjected to quality assessment where the process of data extraction and data analysis was conducted.

Based on the eligibility criteria a total of 13 publications were included and critically appraised as part of this review. This review summarises; the SBDD methods used, their outcome and their impact. The computational, in vitro and/or in vivo results obtained were used to support the success of discovering and developing anticancer therapies for different targets using SBDD.

10 out of 13 publications outlined that SBDD is useful and provided effective results which were proven by in vitro and/or in vivo results. In total 43% of the publications in this study found docking to be the most common SBDD method used for anticancer therapy design and development. Overall, SBDD being a fast and automated process is still considered to be better than the traditional drug design method.

1. Baig MH, Ahmad K, Roy S, Ashraf JM, Adil M, Siddiqui MH, Khan S, Kamal MA, Provazník I, Choi I. Computer Aided Drug Design: Success and Limitations. Curr Pharm Des. 2016;22(5):572-81. doi: 10.2174/1381612822666151125000550
2. Zhang Z, Zhou L, Xie N, Nice E, Zhang T, Cui Y et al. Overcoming cancer therapeutic bottleneck by drug repurposing. Signal Transduction and Targeted Therapy. 2020;5(1). doi: 10.1038/s41392-020-00213-8

When injections go wrong: A rapid review of errors committed when administering and preparing injectable medications in hospitals across multiple countries

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The use of injectable medicines demands competent practitioners and procedures assessed according to evidence-based practices.1 The evidence behind risk assessments are often gained through pharmacovigilance and monitoring incidents to minimise the risks.2,3 This rapid review aims to collate data surrounding incidents reported or observed in the preparation and administration of injectable medications to illustrate areas of risks that are not being addressed to prevent the errors from occurring in the future.

PUBMED, EMBASE and MEDLINE databases were searched. Literature included studies that reported on the frequency and type of errors that occurred when preparing and administering at least one form of injectable medications in a hospital. The studies were appraised using the Joanna Briggs Institute checklist for analytical cross-sectional studies. 845 papers were found and 9 were reviewed in this paper.

The category of errors consistently reported were wrong dose, wrong diluent/ solvent, wrong time and the wrong rate which were reported by 5 of the 9 studies included. Wrong dose errors were reported in 78% of the studies, wrong rate and wrong diluent/solvent in 67% of the studies.

The mean error rate for the intravenous only studies was 58% (95% CI 26 to 90) whereas the studies that included all types of injectable medicines had a mean error rate of 43% (95% CI from -73 to 159). These studies did not have strong associations between error rates and statistical analysis could not be applied to the results in linking errors with their environment, other risk factors or staff characteristics. The aims of these papers were disparate thus were not eligible for a meta-analysis. This review demonstrates the prevalence of

similar errors being reported for injectable medicines across different hospitals, wards and countries. Their complexity in use in clinical areas requires strict aseptic and procedural evaluation to reduce these errors.

1. Lavery I. Intravenous therapy: preparation and administration of IV medicines. Br J Nurs. 2011; 20(4): S28, s30-4.
2. Agency EM. Good practice guide on risk minimisation and prevention of medication errors. 2015.
3. Beaney AMB, A. & Dobson, C.R. & Williamson, S. & Robinson, M. Development and application of a risk assessment tool to improve the safety of patients receiving injectable medicines. 2005;12: 150-4.

Can glutamate dehydrogenase enzyme immunoassays replace chromogenic culture to detect *Clostridium difficile*? A rapid review

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C. difficile infection causes morbidity and mortality, highlighting the need to optimise detection.[1] Toxigenic culture involves culturing *C. difficile* on agar, identification and testing of colonies for the presence of toxins. Toxigenic culture is the preferred reference standard for detecting *C. difficile* with a slow turnaround time (TAT) of 48 hours.[2] This is due to culturing on agar, a new chromogenic agar produces a faster TAT of 24 hours.[3] Glutamate dehydrogenase (GDH) enzyme immunoassays (EIAs) produce results in 2.5 hours improving patient health outcomes.[4] Comparison of GDH EIAs and chromogenic culture will conclude whether GDH EIAs can replace the need to culture without compromising on accuracy. This is followed up by identification and testing for toxins.

Medline, Web of Science, Scopus and EMBASE identified literature comparing GDH EIAs and chromogenic culture. The literature was screened for eligibility using pre-determined questions, inclusion and exclusion criteria. The quality and bias were analysed using CASP and Joanna Briggs Institute checklists.

159 papers were screened to 7. In 5 papers a comparison was made to one test and chromogenic culture was the most sensitive at 100%, GDH EIA values ranged from 87.5% to 100%. In 3 papers a comparison was made to two or more tests and GDH EIAs was the most sensitive in 2 papers at 71.2% and 88% while chromogenic culture was 67% and 70%. Chromogenic culture was the most sensitive (99-100%) in 1 paper.

GDH EIA is the most sensitive test because when two or more comparison tests were used it displayed greater sensitivity. Two or more comparison tests improved data reliability. When comparing sensitivities in the future multiple tests should be utilised as a comparison to a new diagnostic test. The result of the comparison tests and the new test will determine a true positive.

1. Martinez-Melendez A, Camacho-Ortiz A, Morfin-Otero R, Maldonado-Garza HJ, Viiiarreai-Trevino L, Garza-Gonzaiez E. Current knowledge on the laboratory diagnosis of Clostridium difficile infection. World J Gastroenterol. 2017;23(9):1552-67. doi: 10.3748/wjg.v23.i9.1552
2. Crobach MJT, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2016;22:S63-S81. doi: 10.1016/j.cmi.2016.03.010
3. Park KS, Ki CS, Lee NY. Isolation and identification of Clostridium difficile using ChromID C. difficile medium combined with Gram staining and PRO disc testing: A proposal for a simple culture process. Ann Lab Med. 2015;35(4):404-9. doi: 10.3343/alm.2015.35.4.404
4. Moon H-W, Kim HN, Hur M, Shim HS, Kim H, Yun Y-M. Comparison of Diagnostic Algorithms for Detecting Toxigenic Clostridium difficile in Routine Practice at a Tertiary Referral Hospital in Korea. PLoS ONE. 2016;11(8):e0161139. doi: https://dx.doi.org/10.1371/journal.pone.0161139

How Effective are All Wales Therapeutic and Toxicology Centre's National Prescribing Indicators in Improving Quality of Care in Wales? A Closter Look into Rationale and Outcomes.

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The All Wales Therapeutics and Toxicology Centre (AWTTC) has implemented a set of recommendations for primary care prescribers, called national prescribing indicators (NPIs), with the aim of promoting safer, evidence-based prescribing.[1] The need for evidence-based best-practice arose from the increased prevalence

of inappropriate prescribing and insufficient tasting in an aging population in which many suffer from co-morbidities. The aim of this study was to examine the evidence that drives the need for implementing the NPIs, while analysing primary care prescription data. The focus of the study was six NPIs relating to chronic kidney disease and cognition.

Available literature was investigated for evidence to support the need for NPIs. Quantitative prescribing data, extracted from the NHS Informatics Services (NWIS), was then analysed to explore the nature of prescribing in Wales, look for trends and assess the effect of introducing NPIs on prescribing habits. Other sources like health board formularies and Public Health Wales Observatory were needed to find more information to contextualise NWIS data.

The amount of data collected for most NPIs is not enough to be able to make meaningful assumptions about the effects of NPIs on prescribing habits. However, it was valuable for recognizing similarities and differences in treatments in different areas of Wales, requiring more research into potential causes for discrepancies.

A link between social deprivation in areas and the prescribing of antipsychotics and excess use of anticholinergics was found during the research. Further investigation into the causes of disparity is required to ensure equality. Other potential reasons for disparity could be the number of general practices in the health board and their demographics. Subsequent analysis of prescribing data is needed to accurately assess the effectiveness of the introduction of NPIs.

1. National Prescribing Indicators 2020-2021. AWTTC. 2021. [accessed 13 Feb 2021] Available from: https://www.awttc.org/national-prescribing-indicators-2020-2021

Gene therapy in 2020: Nobel prize for the cargo, but what about the vector?

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Gene therapy holds promise for curing incurable diseases that small molecules are failing to address.[1] These include infections, cancers and various genetic diseases. However, therapeutics represented by DNA and RNA are large and hydrophilic in nature calling for a vector to facilitate serum stability and cell entry, for efficient cytosol delivery. Despite 50 years of research the attrition rate between bench and bedside is extremely high and vectors are still falling behind the ultra-large compound libraries.[2] This study investigates vector-specific trends that led successful candidates to clinical trials, to provide a clearer picture of what approaches can benefit future candidates.

Success-bearing tendencies were determined through statistically analysing gene therapy formulations in clinical trials. For this purpose, a table with eligible clinical trials was created, with information being mainly extracted from clinicaltrials.gov database.[3] Data focused mainly on formulation, administration and action related aspects, influencing gene therapeutics' efficacy and safety profile. For data analysis, clinical trials were grouped according to the utilized vector.

Among 122 clinical trials, viruses were the most popular vectors, whereas naked plasmid-DNA electroporation was more common than nonviral vectors. Overall, DNA payloads were more popular than RNA. When it comes to delivery, in situ was preferred to systemic and only viral vectors were preferably or exclusively delivered ex-vivo. In terms of targeted pathologies, non-HIV immunodeficiencies were only treated with viruses and cancers best treated with adenoviruses, retroviruses and naked-DNA.

The study confirmed the hypothesis that no "one-fits-all" vector exists. Even the most popular vector cannot treat the most targeted diseases. Oncogenic retroviruses were the major anticancer candidates while immunosuppressive lentiviruses dominate immunodeficiencies therapy. Similar contradictions demonstrate that literature should not be solely guiding decisions in drug development, without clinical outcomes being considered. Unless a major breakthrough comes along, drug development should be based on optimisation of existing delivery methods by taking example of what works in practice.

1. Gurevich EV, Gurevich VV. Beyond traditional pharmacology: new tools and approaches. Br J Pharmacol. 2015;172(13):3229-41.
2. Collins M, Thrasher A. Gene therapy: progress and predictions. Proc Biol Sci. 2015;282(1821):20143003.
3. Clinicaltrials.gov.2021 [accessed 30 Jan 2021]. Available from: https://clinicaltrials.gov

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A Rapid Review: Do SGLT-2 Inhibitors Have Beneficial Effects in Ischaemic Heart Disease in Patients With Type 2 Diabetes?

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Ischaemic heart disease (IHD) is a leading cause of death in the UK and globally.[1] IHD results in reduced coronary artery blood flow to the heart muscle, starving it of oxygen and metabolic substrates necessary for high energy phosphate production and normal tissue homeostasis. Clinically, IHD most often presents as myocardial infarction (MI) and angina. Type 2 diabetes (T2D) is a major risk factor for the development of IHD. This rapid review focuses on a new class of hypoglycaemic drugs, sodium-glucose cotransporter-2 (SGLT-2) inhibitors in IHD, addressing the hypothesis that SGLT-2 inhibitors have beneficial effects in T2D patients with IHD.

A literature search was conducted using refined search terms across the PubMed and Embase databases (01 January 2005 -- 11 November 2020). Extracted articles were filtered down by removing duplicates, analysis at title and abstract level, and application of *a priori* exclusion/inclusion criteria and the CASP critical appraisal tool. The papers meeting the criteria for full-text analysis were then organised according to study type and relevant data were extracted for narrative analysis.

A total of 1,231 papers were identified of which eleven met the criteria for full-text analysis; six randomised controlled trials and five retrospective cohort studies. There was not sufficient selection/publication bias to warrant exclusion of any of these studies. Eight studies suggested risk reduction in MI and/or major adverse cardiovascular event (MACE) with SGLT-2 treatment. Some studies suggested direct mechanisms of benefit i.e. aiding the heart's ability to withstand and deal with ischaemia (cardioprotective action) independent of glycaemic control.

The evidence from this review supports the hypothesis that SGLT-2 inhibitors have beneficial actions in IHD. However, it is unclear whether the benefit is through reduction of event risk or through the heart's greater ability to withstand ischaemia and reduction of ischaemia/reperfusion injury. More research is needed to confirm the relationship between SGLT-2 inhibitors and IHD in T2D.

1. BHF CVD statistics UK factsheet 2020 edition. British Heart Foundation; 2020

Demographics, features and characteristics related to single tricyclic antidepressant (TCA) ingestion enquiries to the National Poisons Information Service (NPIS) from 2014 to 2020 in England and Wales

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Tricyclic antidepressant (TCA) is a class of antidepressants that are known to be toxic in overdose. However, they are still being prescribed for depression and non-depression conditions in children and adults.1 This study investigates recent data of poisoning in England and Wales involving TCAs and the factors that lead to their overdoses. TCA poisoning deaths recorded in the Office of National Statistics (ONS) and their prescribing trends are also analysed.

The primary data used for this study were poisoning cases recorded on the UK Poisons Information Database (UKPID) based on enquiries from healthcare professionals to the National Poisons Information Service (NPIS). Out of 3131 cases recorded related to TCAs, 1702 were obtained from the screening process, including single TCA overdoses and other eligibility criteria.

The findings showed that the cases of poisoning are most commonly seen involving amitriptyline (n=850). Patients commonly presented to hospitals were females (n=662) and people aged 20 to 29 (n=176). The common cause of poisoning was intentional (n=579), followed by therapeutic error (n=252). The reasons for poisoning differ in different age groups ($p<0.01$). 52% of the patients presented with no symptoms (n=529), and 34% experienced minor symptoms (n=339) throughout the time they were poisoned. However, 90% of severely poisoned patients (n=68) have ingested TCAs deliberately for self-harm.

The prescribing trend of TCAs increased from 2014 to 2018. Nevertheless, the number of poisoning cases and deaths have declined over the years studied. The prescribing of TCAs and the number of deaths showed a strong negative correlation. This may mean that TCA prescribing is now mostly for non-depression conditions, and it is essential that this decrease is maintained. However, the high proportion of intentional ingestions implies that the underlying cause needs to be investigated. Additionally, strategies must be implemented to manage therapeutic errors from occurring.

1. Hoffman RS, Howland MA, Lewin NA, Nelson L, Goldfrank LR, Flomenbaum N. Goldfrank's toxicologic emergencies. Tenth edition. ed: New York ; London : McGraw-Hill Education; 2015.

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

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Almost 80% of lower limb amputations are caused by diabetic foot ulcers.[1] *Staphylococcus aureus* is one of the most common pathogens isolated from diabetic foot ulcers and known to express genes that instigate biofilm formation.[2] Research has shown that biofilms evade bacterial eradication from antibiotics and host defence mechanisms.[1-3] Biofilms are identified in different types of infections including chronic wounds,[3] displaying higher resistance to antibiotics compared to free-floating bacteria.[1, 3] This rapid review aims to review and critically analyse available literature to determine how biofilms of the bacterial species *S. aureus* affect wound healing in diabetic foot ulcers.

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

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

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

2. Pouget C, Dunyach-Remy C, Pantel A, Schuldiner S, Sotto A, Lavigne J-P. Biofilms in diabetic foot ulcers: significance and clinical relevance. Microorganisms. 2020;8(10):1580. doi: 10.3390/microorganisms8101580
3. Dunyach-Remy C, Ngba Essebe C, Sotto A, Lavigne J-P. Staphylococcus aureus toxins and diabetic foot ulcers: role in pathogenesis and interest in diagnosis. Toxins (Basel). 2016;8(7):209. doi: 10.3390/toxins8070209
4. Metcalf DG, Bowler PG. Biofilm delays wound healing: A review of the evidence. Burns Trauma. 2013;1(1):5-12. doi: 10.4103/2321-3868.113329
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. doi: 10.1136/bmj.b2535

Evaluation of the mechanism of actions of Rycals, novel therapeutic compounds for the treatment of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic arrhythmogenic disorder characterised by ventricular tachycardia as a result of β-adrenergic stimulation after physical or emotional stress.[1] The most prevalent form of CPVT (CPVT1) is caused by mutations in the cardiac ryanodine receptor calcium release channel (RyR2).[2] These mutations result in RyR2 becoming ‘leaky’, resulting in inappropriate

calcium release during diastole and thus arrhythmia generation.[1] Treatment for CPVT isn't always adequate, and so research is underway to investigate new prospective pharmacological treatments. Rycals are a novel class of drugs which have been proposed to minimise or suppress this Ca^{2+} leak evident in CPVT and related arrhythmogenic disorders. The mechanisms by which they achieve this are a source of debate in the field and were assessed in this review. The aim was to evaluate Rycals as arrhythmia therapy, and their mechanisms of action on RyR2 dysfunction in CPVT and heart failure settings.

Literature searches were conducted using the databases Medline, Embase and Scopus, and the records were exported into EndNote X9. Articles were reviewed against pre-defined inclusion and exclusion criteria. Critically defined data were extracted and studies were critically analysed using an adapted CASP framework.

Rycals' proposed mechanisms of action were assimilated into themes and evaluated. The leading theory of Rycals promoting FKBP12.6 (a RyR2 accessory protein) binding in order to stabilise channel closing was found to be questionable, with alternative theories such as correcting of 'unzipping' and targeting of RyR2 opening properties seeming more credible. Models and techniques were appraised and it was evident that more suitable models are required for CPVT research; development of human-induced pluripotent stem cell (hiPSC) derived cardiomyocytes is key.

Rycals are a valid candidate for anti-arrhythmia therapy. All studies evaluated showed that use of Rycals results in a reduction in calcium release, regardless of their mechanism.

1. Kim CW, Aronow WS, Dutta T, Frenkel D, Frishman WH. Catecholaminergic Polymorphic Ventricular Tachycardia. Cardiol Rev. 2020;28(6):325-31. doi: 10.1097/crd.0000000000000302
2. Pérez-Riera AR, Barbosa-Barros R, de Rezende Barbosa MPC, Daminello-Raimundo R, de Lucca AA, de Abreu LC. Catecholaminergic polymorphic ventricular tachycardia, an update. Ann Noninvasive Electrocardiol. 2018;23(4):e12512. doi: 10.1111/anec.12512

Tricyclic Antidepressants (TCAs) and the Associated Safety Concerns and TCA Toxicology Features and Treatments

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Tricyclic antidepressants (TCAs) are effective in treating depression, but due to worries of toxicity in overdose, there has been a decline in the number if TCAs prescribed for depression. The use of TCAs has decreased, thus increasing other classes of antidepressants such as SSRIs.[1] The presence of other indications like neuropathic pain has continued TCA prescribing.

The aim was to study the changes in the prescribing of TCAs, the TCA-related deaths and the UKPID TCA ingestion enquiries. The UKPID TCA poisoning enquiry cases were filtered to obtain single TCA agent cases. Data related to the number of TCA ingestion cases, TCA toxicology characteristics and the treatments were analysed.

There two notable results in the prescribing data were the steady increase in the prescribing of amitriptyline and the rapid decline in the prescribing of dosulepin. The TCA related mortality data presented decrease in TCA poisoning related deaths over 26 years. A total of 817 single ingestion TCA enquiry cases were identified, and of these 817 cases, 53% of patients were asymptomatic, 44% were symptomatic, and 3% had unknown features.

There were 91 different features identified, and of these features, the cardiovascular features were the most commonly recorded, thus indicating that cardiovascular features are associated with TCA poisoning. It was confirmed by previous research on TCA poisoning and cardiovascular toxicity, which reported fatality in TCA poisoning is a consequence of the cardiovascular features.[2] In regards to treatments, only 27% of patients received treatments and the most frequently given treatment was sodium bicarbonate and which is effective in lessening the cardiovascular toxicity features. Further studies will need to be conducted on TCA ingestion with alcohol and other drugs and the long-term effects of TCA poisoning.

1. Thanacoody R, Antidepressant and antipsychotic poisoning. Medicine 2019;48(3):194-196. doi: https://doi.org/10.1016/j.mpmed.2019.12.012
2. Thanacoody HK, Thomas SH. Tricyclic antidepressant poisoning: cardiovascular toxicity. Toxicol Rev. 2005;24(3):205-14. doi: 10.2165/00139709-200524030-00013. PMID: 16390222.

A rapid review of the validation assays performed on three-dimensional skin models for use in dermatological research

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The skin is a complex, multi-layered organ. Therefore, identifying when it has been sufficiently replicated in-vitro is problematic, hence challenging researchers when attempting to validate bioengineered skin models. This rapid review outlines the immunohistochemical (IHC) assays necessary to generate a reliable skin model for use in research.[1,2] A recommendation for these assays will be provided to Cardiff School of Pharmacy and Pharmaceutical Sciences' skin laboratory.

Three databases (EMBASE, MEDLINE and Scopus) were searched for literature where IHC assays tested three-dimensional in-vitro skin. PRISMA protocols were followed using predefined selection criteria.[3] Studies were screened for only healthy, human, three-dimensional skin models. Full-text English-language studies were then carried forward. These studies were critically appraised using relevant CASP criteria[4], and only satisfactorily trustworthy studies were included in the review.

Eight studies were obtained, and a table of recommendations was developed. Results suggested that a selection of IHC proliferation, differentiation and penetration assays were required. The expression of relevant markers would only be seen in specific skin layers. Findings propose that cadherin-1, claudin-1 and zonula occludens-1 should be expressed throughout the epidermis. Filaggrin-1 and loricrin are differentiation markers expected in the stratum granulosum. Whereas, involucrin and keratin-10 should be in the stratum spinosum. Proliferation marker Ki67 should be found in the stratum basale, as would differentiation marker keratin-14. Collagen-4 expression suggests formation of a basement membrane, and collagen-1 implies an appropriately differentiated dermis. Presence of all these markers signify that a reliable in-vitro skin model has formed. These recommendations were made to the skin laboratory.

This review does not produce a gold-standard proposal for the histochemical characterisation of in-vitro models. However, it does suggest the minimally required markers that researchers should identify in their bioengineered models before use in further research. Therefore, a full systematic review is required before models can be appropriately standardised.

1. Vijayavenkataraman S, Lu WF, Fuh JY. 3D bioprinting of skin: a state-of-the-art review on modelling, materials, and processes. Biofabrication. 2016;8(3):032001. doi: http://dx.doi.org/10.1088/1758-5090/8/3/032001
2. Derr K, Zou J, Luo K, Song MJ, Sittampalam GS, Zhou C, et al. Fully Three-Dimensional Bioprinted Skin Equivalent Constructs with Validated Morphology and Barrier Function. Tissue Engineering - Part C: Methods. 2019;25(6):334-43. doi: 10.1089/ten.tec.2018.0318
3. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097-e. doi: 10.1371/journal.pmed.1000097
4. CASP. CASP Checklists. 2020 [accessed 25 February 2020]. Available from: https://casp-uk.net/casp-tools-checklists/

The efficacy of MDMA for the treatment of neuropsychiatric diseases: rapid review and prospects for routine clinical use in the U.K.

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MDMA (*3,4-methylenedioxy-methamphetamine)* is a well-known psychoactive stimulant of the central nervous system, commonly known as *Ecstasy* and used for recreational purposes.[1] Many pre-clinical and clinical studies have shown that MDMA induces positive psychological effects, including a positive pro-social effect, increased interpersonal trust and an improved emotional empathy.[2,3] This rapid review aims to gather and evaluate current evidence on MDMA's potential as a therapeutic, focusing on clinical trial data.

EMBASE, MEDLINE, APA PsycInfo and Clinicaltrials.gov were searched for randomised, double-blinded, placebo controlled clinical trials which assessed the use of MDMA to treat stress-related and mood disorders. Studies were screened against pre-determined eligibility criteria for inclusion in the rapid review. Data were extracted and analysed from included papers, which include the studies' characteristics, primary outcome measures, and safety data. Studies were critically appraised for potential sources of bias using Cochrane's revised risk-of-bias tool.

A total of seven studies were included in the rapid review after screening. All studies assessed the effectiveness of MDMA-assisted psychotherapy (MDMA-AP) instead of monotherapy. Six studies assessed MDMA-AP for post-traumatic stress disorder, while one study assessed social anxiety in autistic adults. Overall, the studies found MDMA-AP to be more effective than placebo, with a combined mean effect size: Cohen's d = 1.22. Most adverse events found were minor, with only one significant adverse event found potentially attributable to MDMA.[4]

Clinical trial data have demonstrated MDMA's effectiveness when used in conjunction with psychotherapy. However, all studies found were Phase 2 clinical trials with low sample sizes. This exemplifies the need for larger clinical trials to ascertain MDMA's effectiveness and safety. Many barriers hinder MDMA research and potential for routine clinical use, especially in the UK. These include legal issues, cost, political barriers, and public perception. These barriers could be eased as more studies shed light on MDMA's therapeutic potential.

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Exploring Trends in Non-Medical Independent Prescribing in Primary care in Wales

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The number of healthcare professionals gaining prescribing rights are growing, with the aim to improve patients' access to care and better utilise healthcare professionals' knowledge and skills.[1] Welsh Government policies have focused on enhancing primary care where implementation of primary care clusters within the local health boards (LHBs) have been drivers for the implementation of non-medical independent prescribers (NMIPs).[2] This has resulted in a large increase in the number of NMIPs practicing in primary care in recent years.[3] There is limited literature surrounding non-medical independent prescribing trends. This study investigates the volume of prescribing in each LHB, and the therapeutic areas prescribed.

A retrospective secondary data analysis of prescribing trends obtained from the Comparative Analysis System for Prescribing Audit (CASPA) from April 2011 to March 2020 was conducted to compare changes in prescribing volume (number of items) across LHBs. CASPA data were categorised into British National Formulary (BNF) chapters and a pareto analysis[4] determined the most prescribed therapeutic areas. These accounted for 75% of total prescribing, which was used for further analysis.

Non-medical independent prescribing volume had increased (404%) over the research period with the largest prescribing increase after 15-16. The largest proportion of total prescribing was in Betsi Cadwaladr University Health Board (33%). The therapeutic areas where NMIPs were prescribing the greatest number of items in 11-12 were anti-infectives and respiratory. Anti-infectives were the most prescribed in five out of the seven LHBs. In contrast, by 19-20 cardiovascular and central nervous system items were the most prescribed for all LHBs.

NMIP prescribing is increasing across Wales and within each LHB, however, inconsistencies between LHBs are apparent. An identified prescribing shift in therapeutic areas suggests NMIPs are more involved in the management of chronic conditions. However, study limitations require further work to explore the identified trends further.

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Do sodium glucose cotransporter 2 inhibitors have a beneficial effect in chronic heart failure and go beyond blood glucose control in diabetes? A rapid review

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Despite recent advances in Heart Failure (HF) therapies, mortality and morbidity remains high.[1] Cardiovascular outcome trials showed that some sodium glucose cotransport 2 inhibitors (SGLT2is) proved to be effective at reducing cardiovascular death, and in particular, reduce hospitalisation for HF in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease.[2] This encouraged research into the use of SGLT2is in patients with characterised HF and without T2DM, and so the aim of this study is to determine whether SGLT2is are beneficial in all HF patients, regardless of diabetic status.

This review was conducted in accordance with the Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. An electronic literature search was conducted using the databases PubMed, Medline and Embase. The study focused on randomised controlled trials (RCTs) and their subsidiary analyses, and the Cochrane tool for assessing the risk of bias was used to critically appraise studies.

Results identified five RCTs, and ten additional or subgroup analyses of the two largest RCTs included in the review. All five RCTs were deemed to be at low risk of bias. Results from these studies showed that SGLT2is had a beneficial effect in reducing a composite of cardiovascular death and hospitalisation for HF (HR 0.74 [95%CI 0.65-0.85]), as well as improving patient-reported quality of life (OR 1.18 [95%CI 1.11-1.26]).[3]

SGLT2is were associated with a reduction in clinically important HF related outcomes, notably hospitalisation for HF. These benefits were seen regardless of the absence of T2DM, and so the findings suggest that the decision to prescribe SGLT2is in HF should not be determined by glycaemic status, and that there is a need for these agents to be incorporated into HF guidelines. The exact mechanism by which SGLT2is exert these pleiotropic effects remains undetermined, and further studies are required to elucidate this.

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Retrospective data analysis on antibiotic prescribing in Out-Of-Hours setting in Betsi Cadwaladr University Health Board

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Antimicrobial resistance is driven by inappropriate prescribing of antibiotics.[1] Out-Of-Hours (OOH) has been identified as an area of increased prescribing of antibiotics, particularly broad spectrum, however there have been no studies looking at OOH antibiotic prescribing in Wales specifically.[2] The aim of this study was to assess the appropriateness of antibiotic prescribing and identify areas where increased antimicrobial stewardship measures may be appropriate within the OOH setting in Betsi Cadwaladr University Health Board (BCUHB).

Anonymous CASPA (Comparative Analysis System for Prescribing Audit) data was extracted for OOH services in BCUHB between April 2017 and March 2020, mean quarterly prescribing rates were determined and displayed graphically to determine trends over time.

Total prescribing of antibiotics and of notable broad-spectrum antibiotics stayed mostly level through 2017 and 2018, before drastically increasing in the first quarter of 2019. This increase was sustained through most of 2019, only decreasing in the first quarter of 2020. Notably, there was a particularly large increase in co-amoxiclav prescribing.

No clear reason was identified for the increase in antibiotic prescribing observed, and further research is required into the indication and type of prescriber responsible for the increase to try and identify patterns which can be identified for antimicrobial stewardship. The increase in co-amoxiclav prescribing coincided with a delayed increase in *C. difficile* infections in late 2019.[3] The possibility that this was caused by the increased prescribing of co-amoxiclav is concerning and highlights the urgency for more research in this area.

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Are Zinc Transporters viable targets for Prostate Cancer therapeutic development? A rapid review of scientific literature exploring ZIP and ZnT Transporter activity in Prostate Cancer.

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Zinc is ever presently distributed throughout cells and is heavily involved in the functioning of proteins and cellular processes.[1,2] Cellular zinc is regulated by several protein, most notably zinc transporters. Presently, two zinc transporters families are known: ZnT and ZIP transporters.[1,2] Poor regulation of zinc concentration contributes to a several health-related issues including prostate cancer. Intriguingly, prostate cancer tissue displays a reduction in zinc. Prostate cancer is the second most common cancer amongst men worldwide, with treatment limited to radical prostatectomy with or without radiotherapy.[3,4] This review aims to substantiate the link between prostate cancer and zinc transporter activity, thus, assessing the validity of developing therapeutics targeting zinc transporters.

Relevant literature was obtained from EMBASE, Medline, PubMed, Scopus, and Web of Science with those that met the inclusion criteria being critically appraised and data methodically extracted. Alongside this, the attainment of clinical data from TNM Plot and Oncomine databases were conducted to provide additional context to zinc transporters expression and prostate cancer. The 13 analysed literature covered the expressional alteration of ZIP and ZnT members in non-cancerous and prostate cancer tissue as well as their impact on apoptosis, cell proliferation and invasiveness in prostate cancer cell lines.

Literature pertaining to ZnT's provided no substantial conclusion to their viability as therapeutic targets. ZIP's showed more promise as observations within the studies more consistently matched the clinical data retrieved from Oncomine and TNM than ZnT's. ZIP1 provided the clearest observations based on the magnitude of literature assessing this transporter, leading me to consider it as the most promising target for therapeutic development.

Overall, it seems that other, more plausible avenues for prostate cancer therapies are being explored rather than directly targeting ZIP1 expression. However, if the issue of tissue specificity is overcome, the potential for novel therapeutics targeting these transporters is enhanced.

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Is the ocular surface truly a route for the transmission of COVID-19? A rapid review of clinical evidence

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The novel coronavirus disease COVID-19, caused by SARS-CoV-2, is a growing global health problem with no proven treatment. Studies have described ocular surface involvement with COVID-19 [1,2], implicating a portal of entry and transmission for SARS-CoV-2. The aim of this review was to critically appraise current literature for clinical evidence supporting or refuting the ocular surface, as a route of transmission for SARS-CoV-2 [3] and to evaluate current topical treatments.

Medline, Embase, Scopus and Web of Science were searched for papers published from January 2020 to the 7th of January 2021 and records were extracted into EndNote-X9. Papers were reviewed against a strict inclusion and exclusion criteria to select the most applicable studies. For inclusion a laboratory confirmation of COVID-19 diagnosis was required. Quality and risk of bias was assessed against the Joanna Briggs Institute Critical Appraisal Checklists.

1888 papers were identified (after duplicates were removed) and 23 were included in this review. A meta-analysis could not be completed due to heterogeneity in the methodology of the included studies. The prevalence of ocular manifestations ranged between 3.3 and 58.6% and the rate of detection of SARS-CoV-2 ranged between 0 and 28.5%. Manifestations occurred early at disease onset or later in association with severity. Presence of SARS-CoV-2 was not always associated with ocular manifestations and vice-versa. There is no set protocol for topical treatment.

This review supports the involvement of the ocular surface with SARS-CoV-2, but cannot conclude that it is a true route of transmission. There is an urgent need to develop and evaluate robust and consistent methodology for further research. An awareness of mild conjunctivitis as a prodromal of COVID-19 is of public health interest for early diagnosis and reducing transmission of SARS-CoV-2.

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The Complement Polymorphism C3R102G in Sepsis and its Association with Coagulation: A Rapid Systematic Review and Data Analysis.

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Sepsis is a systemic inflammatory response syndrome in response to infection and a leading cause of death in the UK.[1] The complement system is part of the humoral innate immune response in the blood which helps to clear infections and is excessively overactive in sepsis.[2] C3 is a key protein in the complement system central to activation and amplification[2] C3 is present as a common polymorphism, R102G, where each resulting protein variant either promotes inflammation or risk of infection.[3] This study will determine whether the C3 polymorphism R102G variant is associated with inflammation, infection, and sepsis. Furthermore, complement and coagulation show molecular crosstalk, C3 can be activated by coagulation proteases.[4] Coagulation is also excessively activated in sepsis and it is hypothesised that this molecular link may contribute to sepsis pathology.

A rapid review was undertaken to determine the impact of the C3 R102G polymorphism in inflammation and infection and analysed for coagulation parameters. Genotyping data and clinical parameters from a small cohort study with sepsis patients were analysed for risk association of C3 R102G.

The rapid review and coagulation literature search indicated an association between polymorphism R102G GG (Gly102, F) variant and inflammatory diseases. No association of C3 R102G variants was found with sepsis mortality, and blood protein markers, nor with coagulation parameters.

The rapid systematic review showed a clear association of C3 R102G variant GG (Gly102, F) and inflammation and CC (Arg102, S) with infection. Data analysis confirmed The GG (Gly102, F) genotype produced raised inflammatory and coagulation results. This indicates that it would be worthwhile undertaking a study with a larger cohort. Overall, understanding the risk association of a polymorphism integral to the inflammatory response would enable the stratification of patients with infection, to establish the risk of developing sepsis, and to consider early and targeted treatment.

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Reducing the Damage of Ischaemic Stroke: Design and Synthesis of Brain-Penetrating Prodrugs for WNK Signal Inhibition

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In 2016, the global lifetime risk of ischaemic stroke was over 18% in the over 25s.[1] Neuronal damage is exacerbated by ischaemia-induced oedema, a consequence of electrolyte dysregulation.[2] Electrolyte homeostasis is partially regulated by the WNK-SPAK/OSR1 pathway.[3] While this pathway has potential as a target for antihypertensives[4], it may also be a plausible target for treating oedema following ischaemia.

A literature review was conducted to compare the properties of brain-acting drugs. A second review was then undertaken to understand the various prodrug strategies used to achieve brain selectivity. Suitable techniques were then applied to compatible small molecule WNK signalling inhibitors, using defined criteria. After assessing the relevant properties of these prodrug candidates, synthesis pathways were devised for the three prodrugs deemed most likely to succeed as therapeutics. To do this, similar synthesis schemes from existing literature were adapted.

Typical requirements of crossing the Blood Brain Barrier (BBB) by transcellular diffusion include increased lipophilicity, lower molecular weight (< 400Da) and non-substrates of P-glycoprotein. Six prodrug strategies were identified. Four presented a method to cross the BBB. The remaining two offered solutions to maintain exclusive drug activity in the brain. Six prodrug structures were designed, using two of the initial six prodrug strategies.

Prodrugs may present a feasible solution to achieve exclusive WNK-inhibition activity in the brain.

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Investigating the efficacy of psilocybin for the treatment of anxiety and depression: a rapid review and prospects for routine clinical use in the U.K.

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Psilocybin ([3-(2-Dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate) is the hallucinogenic compound found in fungi, commonly known as magic mushrooms, and used for recreational purpose.[1] Many studies have shown that psilocybin induces psychedelic effects and a controllable altered state of consciousness that may be beneficial in neuropsychiatric illness.[2] This rapid review aims to collate and analyse current evidence on psilocybin's potential as a therapeutic agent and barriers to its routine clinical use in the UK.

PubMed, Scopus, Embase and Clinicaltrials.gov were searched to find literature evidence of psilocybin being trialled as a treatment for anxiety and depression. Studies were screened for their eligibility against pre-determined inclusion and exclusion criteria. Included studies were subjected to quality assessment and critical appraisal using a Mixed Methods Appraisal Tool. Data including studies' characteristics, primary outcome measures and safety data were manually extracted for analysis and compilation.

A total of six reports were included in this rapid review based on their eligibility criteria. Instead of monotherapy, all included studies considered the effectiveness of psilocybin-assisted psychotherapy (psilocybin-AP). Four studies assessed psilocybin-AP in patients with cancer diagnoses and anxiety or depression, one in patients with treatment resistant depression, and another in patients with major depressive disorder. Narrative synthesis summarises each of these trials and outcome data demonstrate a large effect size of psilocybin-assisted therapy on anxiety and depression. All adverse effects were found to be transient and tolerable, with no long-term adverse effects at 4.5 years.[3]

These trials have shown psilocybin's efficacy when used with psychotherapy, however all studies found were small scale, Phase 2 trials. This review demonstrates that further studies need to be conducted with larger sample sizes, better blinding procedures and study design that does not include crossover. There are many barriers to psilocybin's routine clinical use in the UK. These include its classification, cost, and public perception.

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Exploring final year pharmacy student views on Cardiff University's MPharm based on NSS free text comments in the period 2017 to 2020

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The National Student Survey (NSS) is a United Kingdom (UK) wide survey that collects the opinions of final year undergraduate students. Universities use their students' NSS free text comments to improve student satisfaction.[1] Although Cardiff University's Master of Pharmacy (MPharm) have analysed NSS free text comments previously, this is the first time free text comments were analysed over a period of years. The aim of this study was to explore the free text comments from Cardiff University's final year pharmacy students between 2017 and 2020 to suggest improvements and provide feedback to Cardiff University's MPharm.

Conventional content analysis and direct content analysis of NSS free text comments from Cardiff University's final year pharmacy students between 2017 and 2020 was employed.[2]

A total of 415 final year students at Cardiff University's MPharm were able to complete the NSS between 2017 and 2020. Of which a total of 190 students provided free text comments in this period, relating to positive or negative views on their experiences (45.8%). A total of 14 themes emerged from the conventional content analysis. The themes 'staff', 'course' and 'student support' had the most positive comments. While the theme 'assessment' had the most negative comments which decreased significantly over the four years. The themes with the most negative comments for students in 2020 were 'timetable', 'course', 'placement', and 'assessment', respectively. Cardiff University should consider maintaining and improving the organisation of the MPharm, especially the timetable. Staff made a positive impact on students' experiences in terms of support, both academically and pastorally. In addition, students have expressed the need for clinical support, especially more placements.

Students' comments may be affected by external and internal factors.[3] Cardiff University should consider the suggestions made in this study in addition to other materials to help aid decision making on the MPharm.

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A rapid review of histone deacetylase inhibitor in Breast Cancer Treatment and therapy

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Breast cancer is one of the most common type cancers among women globally. Breast cancer can also affect males.[1] It is comparatively difficult to diagnosis breast cancer and males usually have poor outcome. With new therapies and advanced diagnostic methods, Breast Cancer is still the most common diagnosed cancer among women globally.[2] The development of Cancer cell usually is controlled by epigenetic process, associating with carcinogenesis. Histone deacetylases (HDAC) is an epigenetic modifier which plays an important role in tumour cell's gene transcriptional activities[3], while normal cells are relatively more resistant to the HDAC inhibitor induced cell death. And hence their inhibitor (HDACi) is so popular in research field, by studying their functional mechanism, anti-tumour effects, potential clinical applications and synergistic effects in combinational treatments.

4 electronic platforms were used: EMBASE, PubMed, Web of Science and Scopus. Searching filters were applied during screening relevant literatures and downloaded into ENDNOTE X9 for further selection. Abstracts were reviewed during first stage. PRISMA flowchart is used for paper selection.

19 papers with 1079 patients confirmed with breast cancer were included in this rapid review. 18 papers were clinical phase I/II trials and only 1 paper was clinical phase III trials. There are no phase 4 trials available up to the date of the report in 2021. Patients enrolled all received prior other treatments and showed an improved survival rate and inhibition of cancer cell development in different degree. 10 papers conducted the trials by using Vorinostat and 3 papers with Entinostat. The only phase III trials were carried with Chidamide.

Although there are many pre-clinical studies on the effectiveness of HDACi against breast cancer, there were limited completed clinical trials with published reports. Most of trials are still ongoing. Findings suggested that there is a higher median PFS in the experimental group, however, the dosage and the adverse event still need to be further worked on with larger scale trials.

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A rapid review of preclinical literature investigating the potential efficacy of hydrogels as local drug delivery systems for glioblastoma multiforme therapeutics

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Glioblastoma multiforme (GBM) is the most common form of primary brain cancer.[1] The prognosis of GBM is very poor, with a median survival time of 14.6 months.[2] Treatment is very complex, with the blood-brain barrier (BBB) being the main obstacle. Local drug delivery bypasses the BBB, allowing chemotherapeutics to be delivered directly to the cancer site.[3] This rapid review aims to assess the potential efficacy of hydrogels as local drug delivery systems for GBM.

Three databases were searched, and pre-determined inclusion and exclusion criteria were followed to ultimately give seven papers for analysis. All included studies investigated hydrogels, used preclinical rodent brain cancer models and had an untreated control. Survival data were extracted, and the median survival ratio was calculated. The quality of the papers was assessed against a 12-point quality assessment score.[4]

The results showed that hydrogels were safe and effective in the brains of rodents. In all papers, drug- loaded hydrogels prolonged animal survival in comparison to an untreated control. Long-term survivors were reported in all but one of the papers. In combination with adjuvant radiotherapy, oral temozolomide and/or local temozolomide, hydrogels produced even greater survival outcomes.

These results show that hydrogels have the potential to be efficacious local drug delivery devices for GBM therapeutics. Hydrogels were shown to be versatile and with more favourable physical characteristics than the already approved local drug delivery device, Gliadel. Included studies were preclinical but they provide rationale for further progress towards clinical investigations.

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An evaluation of the 'Independent Prescribing for Acute conditions' service in Betsi Cadwaladr University Health Board

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Pharmacist independent prescribing was introduced in 2007 in Wales[1] with the aim of improving patient care by increasing patient choice in accessing medicines, making better use of health professionals' skills, and making it easier for patients to get the medicines they need.[2] Since its introduction, uptake of independent prescribing within community pharmacy has been low.[3] However, the current drive from the Welsh Government to deliver care locally with one independent prescribing pharmacist working in every community pharmacy by 2030,[4] has meant that more services are being set up within community pharmacy in Wales to meet this goal. This study aims to evaluate the 'Independent Prescribing for Acute Conditions' service offered by community pharmacists in Betsi Cadwaladr University Health Board.

A retrospective secondary analysis of data captured from contractors in the health board offering the service between September 2019 and September 2020 was used to evaluate the service. The data was consolidated into one Microsoft Excel® spreadsheet and then cleaned, coded and descriptively analysed.

Over the study period, 2801 consultations were carried out by a total of eight contractors (nine community pharmacist independent prescribers). The most common conditions treated were disorders of the respiratory system (33.3%, n=920). A total of 2285 items were prescribed over the time frame, most of which were antibiotics (42.4%, n=968).

The number of consultations and prescribers offering the service have increased over the time frame suggesting that there has been good uptake. The majority of the presenting complaints treated were for acute minor conditions, illustrating that the aims of the service were met. The findings suggest that the service has been successfully implemented and has huge potential in meeting the Welsh Government's agenda to expand independent prescribing within community pharmacy across Wales.

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Exploring antimicrobial prescribing behaviours in primary care during the COVID-19 pandemic

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On 11 March 2020, WHO declared COVID-19 a pandemic.[1] To reduce transmission, primary care services within the UK changed to be conducted remotely. Around 80% of antibiotics in the UK are prescribed in primary care; therefore, it is important to investigate how the change in service provision has impacted the prescribing of antibiotics and in turn, the increasing threat of antimicrobial resistance.[2] This study aims to explore the antimicrobial prescribing behaviours of GPs during the first wave of the pandemic.

GPs working within several Welsh health boards were invited to take part in an online cross-sectional survey. The survey contained a range of open and closed questions regarding remote consultations and the impact on antibiotic prescribing, with a particular focus on respiratory tract conditions. Quantitative data were statistically analysed and inductive thematic analysis was used for the qualitative data.

The majority of participants believed that the frequency at which they prescribed antibiotics has changed since the pandemic, with some GPs commenting they would be more likely to issue antibiotics when consulting remotely. Most participants found that remote consultations made diagnosing/managing respiratory tract infections more difficult. GPs also stated that antimicrobial stewardship programmes had been interrupted due to COVID-19, with two main suggestions to improve this being more GP guidance and patient education.

Most initial consultations were conducted over the telephone, followed by in-person. Prescribers identified concerns regarding remote consultations and their negative impact on stewardship, therefore, antimicrobial resistance. A study in 2018 found it was often respiratory tract infections that contributed to inappropriate prescribing leading one to wonder if they are the leading cause.[3] This research also identified a variation in GP confidence levels, with recommendations that more training could improve this. Long-term studies looking at the effect of the pandemic on antimicrobial resistance are necessary to understand the need for adaptations to current stewardship programmes.

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Inhibitors of protein-protein interactions as an innovative strategy to develop anti-influenza drugs: a rapid review

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Vaccines and antiviral therapeutics represent the current arsenal used to fight influenza virus infection [1]. Among the available drugs to treat influenza virus infection, neuraminidase inhibitors are the only class of drugs prescribed in the UK [2], as M2 ion channel blockers are no longer recommended because of the emergence of drug resistance. Protein-protein interaction (PPI) inhibitors are an attractive new class of anti-influenza compounds which are currently in preclinical stages of development. Increasing evidence shows that these inhibitor types have a high barrier to drug resistance [3]. The aim of this review is to evaluate the most promising PPI inhibitors and identify any which show potential for translation into clinical trials.

This rapid review was conducted in compliance with PRISMA guidelines. A well-defined search strategy was applied to three different databases (PubMed, Scopus and Web Of Science). As crucial PPI crystal structures were released at the end of the 2000s, articles published before 2010 were excluded. To focus the research on specific antiviral agents, only inhibitors that targeted viral-viral PPIs were included. All papers that fulfilled the predetermined eligibility criteria were included in this rapid review and relevant data were extracted.

Twenty-three articles were selected in this study and reported inhibitors of five different PPIs of influenza virus: M1-M1, NP-NP, NP-PA, PA-PB1 and PB1-PB2. All the selected compounds possessed specific anti-influenza activity *in vitro* and five of them exhibited very high selectivity indexes (>350). Some of the most promising inhibitors showed *in vivo* anti-influenza activity and a reduced propensity to develop drug resistance compared to current licensed antiviral therapeutics.

These inhibitors proved to be promising candidates for the treatment of influenza virus infections, and could reduce the issue of antiviral resistance. Future research should further characterise *in vivo* activity and ADME profiles of these candidates using standardised assay models.

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A rapid review on the dosing recommendations of fat-soluble vitamins in long-term parenteral nutrition

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Parenteral nutrition (PN) is a lifesaving therapy that allows patients, typically with malabsorptive disease states, to obtain the right balance of nutrients and electrolytes such as fat-soluble vitamins.[1] As long-term (LT) PN becomes seemingly prevalent, it is important to ensure that patients are receiving optimal doses of vitamins A, D, E and K to reap their benefits as well as avoid harmful effects.[2] This rapid review aims to investigate the existing literature on the provision of vitamins A, D, E and K in long-term (LT) PN patients and provide recommendations on how to optimise fat-soluble vitamin dosing.

A search of EMBASE, SCOPUS and PubMed databases was conducted during October 2020 using a refined list of search terms. LT PN was defined as a mean PN duration of all patients that was longer than 3 months. Articles were imported into EndNote and screened against a list of inclusion and exclusion criteria and then critically appraised.

Out of the 1917 results returned, 10 final papers were identified and selected for the review. The majority of studies were low in quality, most being case series, however it was apparent that there was a lack of research done in this specific area. Nonetheless, the review found suboptimal fat-soluble levels to be a common trend amongst LT PN patients, especially for vitamin D provision.

The dosing of fat-soluble vitamins needs to be sufficient to ensure patients are within the recommended range. Standardised guidelines with standardised definitions of deficiency are required to instruct healthcare providers on the correct dosing, monitoring and procedures if a patient falls out of range. Multi-centre studies with a larger sample size are needed to provide generalisable data and validated recommendations.

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Does Src inhibition enhance trastuzumab therapy in HER2-overexpressed breast cancer?

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Overexpression of human epidermal growth factor receptor 2 (HER2) limits endocrine response and adversely affects prognosis of patients with metastatic breast cancer[1]. Although Trastuzumab is currently first-line treatment for early and advanced disease[1-2] and has some benefit, resistance hinders survival rate as patients demonstrate a median response of less than 1 year[3]. Thus, there is a drive for the development of more effective treatments for these tumours. Src, a non-receptor tyrosine kinase that acts as a common upstream regulator of signalling cascades, including those involved initiated by HER2 and implicated within trastuzumab resistance. This review aimed to determine whether Src inhibition alongside trastuzumab treatment within a combination therapy represents an effective therapy regimen for ER+/HER2+ and ER-/HER2+ breast cancers.

Three bibliographical databases were consulted – EMBASE, MedLine and Scopus – to retrieve evidence encompassing preclinical efficacy of combination therapy. Studies were screened for eligibility according to inclusion and exclusion criteria. Of 1382 studies identified, 10 relevant studies to be included within the review. Relevant studies were subjected to quality assessment, using an adapted CASP checklist, before study data was extracted and collated. This review summarises the effect combination therapy upon proliferation, apoptosis and cell cycle arrest *in vitro* and proliferation *in vivo* in comparison to trastuzumab and Src inhibition monotherapies.

Within ER+/HER2+ and ER-/HER2+ *in vitro* models, studies revealed the ability of combination therapy to decrease cell survival and increase apoptosis and cell cycle arrest more effectively than monotherapies. These observations were supported by *in vivo* studies that demonstrated tumour regression within ER+/HER2+ models using combination therapy, an antitumour effect that was not seen using monotherapies.

This suggested that Src inhibitors can enhance the cytotoxic effect of trastuzumab therapy. Therefore, the use of Src inhibitors with trastuzumab therapy may represent an effective strategy to treat HER2-overexpressed breast cancers and warrants further investigation.

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A rapid literature review on the use of antimicrobials delivered via CADD-Solis (VIP) ambulatory infusion pump or Surefuser+ elastomeric infusion system

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This rapid review is a collaboration with The University Hospital of Wales (UHW). UHW has an ambulatory care unit (ACU) which delivers certain chemotherapy treatments via a CADD-Solis (VIP) infusion pump, a smart-pump technology that is carried around the waist. Benefits of ambulatory care include: reducing the number of overnight hospital stays, and limiting nosocomial infections such as COVID-19.[1] UHW has approached Cardiff University as they would like to incorporate antimicrobials into their ACU with emphasis on the following list: Tazocin, Ertapenem, Amphotericin B, and Ganciclovir. This rapid review aims to search the current literature and assess whether continuous delivery of antimicrobials could be administered via infusion pumps at UHW.

Refined search terms were used to conduct a review of the current literature available in EMBASE, PubMed and Scopus. This literature was exported to the referencing software, EndNote, where a list of inclusion/exclusion criteria, alongside critical appraisal tools were used to select appropriate papers.

The identification and selection of papers led to the inclusion of 10 final publications. The results of this review show that Tazocin and Ertapenem, as well as other antimicrobials from the Penicillin and Carbapenem drug classes, show appropriate stability for use in ambulatory care and have been successfully delivered via elastomeric infusion pumps. No studies were found that mention antimicrobials administered via the CADD device.

To conclude, two of the given antimicrobials have been successfully administered to patients via elastomeric pumps. Therefore, UHW can use the key findings from this review to help them incorporate these antimicrobials into their ACU. Care must be taken when extrapolating data from studies conducted in different countries to ensure that UK safety and stability guidelines are adhered to. Many studies discuss the importance of continuous infusion with antimicrobials in combatting the increasing rise of antimicrobial resistant bacteria.[2]

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ESA therapy in haemodialysis clinical practice: converting patients from short-acting IV epoetin alfa (Eprex) to short-acting s.c. epoetin beta (NeoRecormon) for anaemia of CKD.

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NeoRecormon is a short-acting ESA (Erythropoiesis Stimulating Agent) used in the treatment of Anaemia of Chronic Kidney Disease (ACKD).[1,2] Subcutaneous (s.c.) administration of short-acting ESA reduces ESA

requirement by 20-30%; the longer half-life of s.c. ESA allows less frequent dosing than its intravenous (IV) counterpart.[3] This report evaluates the effectiveness and resource impact of switching haemodialysis (HD) ACKD patients from IV Eprex to s.c. NeoRecormon. The main aims are establishing a Dose Conversion Ratio (DCR); and providing preliminary cost analysis.

This retrospective, longitudinal analysis looks at clinical data (haemoglobin (Hb) values, ESA Mean Monthly Doses (MMDs) and frequencies) from 118 patients across the South West Wales renal medicines service, who were switched from IV Eprex to s.c. NeoRecormon in 2019. Values from the 3-month baseline IV Eprex period (months -3 to -1) were compared to values from an 8-month s.c. NeoRecormon stabilisation period (months 2-8). The ESA 'switch' occurred at month 0. A DCR was calculated (Stabilisation MMD / Baseline MMD) and three subgroup analyses performed.

DCR = 0.8; for every 0.8 IU s.c. NeoRecormon, 1 IU of IV Eprex is required for the same target Hb outcome. This can be expressed as a 20% dose decrease with s.c. administration. At baseline, 74% of patients were in Hb range (100-120g/L) and the average monthly injection frequency was 11.16. During the stabilisation period, 88% of patients were in Hb range, 48% of patients received twice weekly ESA dosing, with an average monthly injection frequency of 7.54.

This data set demonstrates that s.c. NeoRecormon effectively maintains Hb stability in HD ACKD patients converted from IV Eprex. We recommend a DCR of 0.8. The ESA 'switch' shows that s.c. administration of short-acting ESA allows a reduced injection frequency of twice per week; there is no economic disadvantage in switching.

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A rapid review of the provision of fat-soluble vitamins in long-term home parenteral nutrition, and their effect on the stability and dosing of parenteral nutrition.

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Parenteral nutrition (PN) is a means of supplying nutrients intravenously to severely deficient patients, most commonly occurring in those with chronic intestinal failure.[1] PN is typically supplied in pre-mixed bags containing some, or all, required macronutrients, vitamins, and minerals as required. In recent years, growing evidence has been presented to suggest that the components of PN bags are subject to degradation over time in longer-term, at-home patients that require regular monitoring to ensure their needs are met.[2] This rapid review summarises the prevalence of vitamin deficiency-associated health conditions amongst HPN patients, the potential breakdown of these vitamins and the causes, as well as the stability of these vitamins outside of PN formulae.

A total of five databases were analysed, to find relevant literature on the fat-soluble vitamins A, D, E, and K in home parenteral nutrition (HPN). Papers were subsequently screened to ensure adherence to preset inclusion and exclusion criteria, with papers meeting these criteria then subject to critical appraisal for inclusion in the review. Following appraisal, 13 papers were included in the final review, narrowed down from a 40-paper shortlist.

Considerable conflicting evidence was discovered across the papers, with articles both supporting and opposing the theory. Ultimately, the majority of papers pointed to external factors causing the vitamin breakdown, with several indicating no significant breakdown having occurred. These factors included exposure to light, and the adsorption of vitamins to the PN bag surface, amongst others.

Patient responses varied both inter- and intra-study, as well as in the non-human stability focused papers. Consequently, a patient-specific dosage regime would be preferred as opposed to the pre-existing commercially available PN preparations. However, due to both financial and manpower constraints this is not a viable option, with a prioritisation of severely unwell patients being recommended.

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How do different methods of penicillin allergy de-labelling, used by non-specialists in all care sectors, compare: a rapid systematic review

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500,000 people admitted to NHS hospitals each year have a diagnostic label of drug allergy[1]; it is estimated that only 10% of these are truly allergic. Allergy labels are associated with poorer outcomes, longer hospital stays, increased cost and amicrobial resistance. The global mortality associated with antimicrobial resistance is predicted to increase by over 1000% by 2050.[2] Reducing prescribing of restricted antibiotics can help to reduce this. The aim of this paper is to review and critically appraise the literature, identifying and assessing methods of penicillin allergy de-labelling for use by non-specialists in all care sectors.

EMBASE and SCOPUS were searched from January 2000 to December 2020 for a rapid review. Non-English language papers and papers without Penicillin/Beta lactam in the title/abstract were excluded; research articles including an investigation into allergy testing/ de-labelling were included. After screening papers for relevance from their abstract and then full text, papers were critically appraised using the *Joanna Briggs Institute* Critical Appraisal Checklists.

The initial searches yielded 1046 papers which were cut down to 35 for inclusion. Papers were from 14 countries and investigated a range of outcomes e.g. number of patients de-labelled (n=15) and antibiotic usage following intervention (n=14). Results were split into four groups: specific testing methods (n=9), History based interventions (n=11), integrated guidelines and education (n=11), Other (n=4). All papers scored moderately according to the Joanna Briggs Institute checklists with a range of 36%-73%.

It was found that the most effective and safest method of testing is a tiered strategy incorporating taking a structured allergy history and risk stratification, patients can then be either directly de-labelled or tested according to their risk via skin prick testing (higher risk) or provocation tests (low risk). This strategy can be implemented in primary and secondary care with slight adjustments based on the sector.

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An investigation into the depth of knowledge that Welsh community pharmacists have about Inflammatory Bowel Disease and their interactions with IBD patients

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Inflammatory Bowel Disease (IBD) is a chronic complex condition involving modifications to treatment regimens, dependent upon different factors such as severity and disease state (relapse or remission). [1] The effective management of IBD requires a multidisciplinary approach involving many professions. [2] The community pharmacist is one of the most accessible health care professionals (HCPs) [3] yet there is no indication for their role in the management of IBD. This study set out to explore the level of knowledge and the interactions that community pharmacists in Wales have with IBD patients.

A mixed methods approach was utilised. Semi-structured interviews and questionnaires were used as the data collection tools. Non-probability purposive, convenience and snowball sampling were used in the recruitment of participants based on the following inclusion criteria; 1. Practicing community pharmacist 2. Working in Wales. Interview transcripts were thematically analysed to identify themes and sub-themes. Descriptive

analysis of questionnaire data was conducted then used to further support themes emerging from the qualitative data.

Five key themes were identified. Medicine Management, Symptom Management, Knowledge level, Interactions and Development of learning package. It was identified that, although pharmacists were confident with some aspects, such as medicine and symptom management, there was evidence to show that they need a more comprehensive understanding of IBD as a whole. Additionally, pharmacists lacked interactions with IBD patients. An interest in the development of a learning package was identified.

This study concluded that pharmacists lacked knowledge about IBD. There is also a lack of interaction with patients and HCPs about IBD. The data suggests there is greater role for pharmacists to play in the management of IBD. Further studies are required to explore the expansion of the role and its impact.

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Microspheres for local drug delivery to brain cancers: A systematic rapid review of pre-clinical data

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Malignant glioma is an aggressive disease affecting both adults and children. The tumour, especially glioblastoma multiforme (GBM), is resilient against therapies and thus the diagnosis and treatments have made relatively little improvement on prognosis. Advances in the treatment of glioma have remained static since the advent of the currently utilised “Stupp” protocol[1] with local drug delivery implants (GLIADEL wafers) giving little or no benefit.[2] A range of injectable local drug delivery systems, such as microparticles/microspheres, are being developed to overcome some of the limitations of GLIADEL wafers.[3] This systematic rapid review aimed to assess the efficacy of microsphere-drug delivery systems for localised brain cancer treatment in pre-clinical studies.

Web of Science, PubMed and Scopus were searched for relevant pre-clinical animal studies. A total of 15 publications were identified that included 24 experiments overall. Data were extracted from these 24 experimental comparisons; this was divided based on available survival (n=20) and tumour volume (n=4) data. A modified 12-point checklist was utilised for quality and risk of bias assessment.

In general, microsphere-drug delivery systems were found to be efficacious by prolonging survival and reducing tumour growth in both rats and mice. All the 20 studies demonstrated an increase in median survival ratio, and the other four exhibited a decrease in tumour volumes. Some studies combined different local drug delivery strategies (hydrogel + microspheres, wafers + microspheres) and these displayed synergistic effects against the tumour.

The conclusion of this review implies that microsphere-mediated drug delivery seems promising and might present an adjunctive approach to conventional therapies. They are injectable systems and therefore may be able to target inoperable tumours via stereotactic surgery. However, this review provides a systematic overview of the current state of the pre-clinical data in this field and discusses promising developments and future experimental design.

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96.
2. Chowdhary SA, Ryken T, Newton HB. Survival outcomes and safety of carmustine wafers in the treatment of high-grade gliomas: a meta-analysis. J Neurooncol. 2015;122(2):367-82.
3. Bastiancich C, Danhier P, Préat V, Danhier F. Anticancer drug-loaded hydrogels as drug delivery systems for the local treatment of glioblastoma. J Control Release. 2016;243:29-42.

Transition to blended learning as a result of the COVID-19 pandemic: students' experiences on the MPharm degree at Cardiff University

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The COVID-19 pandemic presented significant challenges to the educational sector.[1] In March 2020, many UK Higher Education Institutes (HEIs) closed campuses due to the risk COVID-19 posed to the public. In response to guidance from devolved UK governments, HEIs implemented quick transformations to the way they operated.[2] Before the start of the academic year 2020/21, many HEIs adopted a blended learning (BL) pedagogic approach, a new learning style for many students.[3] This study aims to understand how the COVID-19 pandemic has affected the MPharm student experience in Cardiff School of Pharmacy and Pharmaceutical Science.

A qualitative approach was employed for this exploratory study. Focus group discussions were conducted using Zoom. Students enrolled in MPharm III and IV were invited to take part. Discussions were both video and audio recorded, transcribed verbatim and then analysed thematically to identify key themes.

Six themes arose from the data. The implementation of BL produced a diverse range of opinions. Positives included increased flexibility for learning and a greater level of independence. However, participants identified negative impacts related to communication, including effects on their social contacts, reduced access to instant feedback from academic staff and a lack of confidence in their ability to interact with their peers and academic staff within an online learning environment.

This research allowed Cardiff School of Pharmacy and Pharmaceutical Sciences to gain an understanding of students' experiences on the transition to BL, with the majority of facilitated learning occurring online. Students had to adapt to a new learning style as well as other social restrictions imposed on daily life due to the pandemic. A number of elements of the BL experience could be improved but generally, it was not perceived as detrimental to the overall quality of teaching. Future studies should investigate the students' experiences of MPharm I and II.

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AWMSG Prescribing Safety Indicators: Rationale and Medicines Usage

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In Wales, the All Wales Medicines Strategy Group (AWMSG) produce a set of prescribing safety indicators (PSIs) to identify patients who are at risk of drug-induced harm and enable intervention to proactively prevent harm.[1] These PSIs feed into the Welsh Government's aim of *A Healthier Wales*.[2] The aim of this study was to analyse prescribing data for each of the PSIs across local health boards (LHBs) within Wales and to evaluate their impact on prescribing patterns. This is with a view to assist AWMSG with a strategy (i.e. where should they focus their future attention).

Anonymised secondary care prescribing data was extracted through NHS Wales Informatics Service (NWIS) programme, Audit+ for analysis to be carried out through Microsoft Excel. Analysis was carried out by forming graphs and looking for trends on prescribing habits across the health boards. Prescribing habits observed were compared against evidence found through online and literature searches to generate hypothesis and recommendations.

Analysed data provided an insight into the prescribing habits across the seven LHBs. A major finding for three of the PSIs that all look into anticoagulants was that Hywel Dda health board had only 19% of their patients, on anticoagulants, to have had an anticoagulant review in the last twelve months. [3]

There is a link between the low number of anticoagulant reviews being carried and the high number of patients on an anticoagulant and non-steroidal anti-inflammatory drug (NSAIDs). This study has provided an insight into the prescribing habits which has allowed AWMSG to strategize and to form a targeted action plan within each of the health boards to improve evidence-based prescribing in line with PSIs and minimise patient harm.

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Secondary analysis of the synergistic activity of Pomegranate Rind Extract and Zn (II) ions against *Pseudomonas aeruginosa* and *Escherichia Coli*

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Pomegranates (*Punica granatum* L) have been used in traditional medicine in Europe and parts of South Eastern Asia for thousands of years. Recent investigation has shown extracts from pomegranates to have antimicrobial effects.[1] Further research has shown that this antimicrobial effect can be potentiated by using Zn (II) ions in combination with the pomegranate rind extract[2] (PRE). Unpublished research has assessed this synergy of PRE and Zn (II). The results obtained by these researchers vary to an extent, so this study aims to assess the overall trends shown in their results and potentially explain why the results vary.

Results were provided from unpublished research at Cardiff University, then were used to calculate a geometric mean showing overall trends in the results of both researchers. These global results were then statistically analysed using ANOVA tests and post hoc Turkey tests to establish whether synergy was shown. The initial results from the researchers' work were also analysed to examine the variation between each researcher.

PRE in combination with Zn (II) was shown to have a significantly higher bactericidal effect ($p<0.05$) than PRE or Zn (II) alone at all concentrations tested so synergy was clearly demonstrated. The bactericidal effect observed was greater against *Escherichia coli* than against *Pseudomonas aeruginosa*. There was significant variation found in some of the initial results which does decrease the confidence that the global data is representative of the actual trends.

Results show this research to have promise as synergy is consistently shown for PRE+ Zn (II) against both bacteria, this study also ties in with other research that shows broad spectrum activity at these concentrations against *Herpes simplex* virus and methicillin resistant *Staphylococcus aureus* and methicillin sensitive *S. aureus*. Further research into the mechanism of action could help to provide more information for developing future therapeutics.

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Rapid systematic review and clinical data analysis of the association between a genetic variation of complement factor H and the susceptibility to sepsis and sepsis-related coagulopathy

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Complement Factor H (CFH, FH) is a protein which negatively regulates the alternative pathway of the complement system.[1] Single nucleotide polymorphisms in CFH such as rs1061170 have shown to be associated with chronic inflammatory diseases such as age-related macular degeneration.[2] Little is known

about the correlation between this polymorphism and inflammation or infection or susceptibility to sepsis with excessive complement and coagulation activation. Furthermore, FH is a ligand for several coagulation components and crosstalk is evident[3] and we hypothesise that FH polymorphism could affect sepsis-related inflammation and coagulopathy.

Firstly, a rapid systematic review collated all literature on rs1061170 associated with infection, inflammation or coagulation parameters. Secondly, analysis of sepsis patient rs1061170 genotype and clinical data was used to investigate the susceptibility to sepsis and coagulation parameters.

The rapid review identified 556 records searching Embase, Scopus and PubMed, of which 21 were included in the final review. In a small sepsis patient pilot study, rs1061170 genotype from 38 sepsis and 57 healthy subjects was associated with clinical data. The systematic review results showed that the C allele of rs1061170 polymorphism was associated with lower susceptibility to infectious diseases, while the clinical data analysis determined lower risk of development of sepsis (P=0.094, OR=0.6 and 95%CI=0.33-1.09).

Therefore, considering the future role of genetic stratification in sepsis, a better understanding of this polymorphism is required.

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Are members of the SLC39A zinc transporter family a good target for the treatment and prevention of metastasis? A rapid review.

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A cancer cell's ability to metastasise is arguably the most devastating aspect of the disease, with metastasis being responsible for approximately 90% of cancer mortalities.[1] No therapeutics are currently available for metastasis, meaning the development of a treatment would prove revolutionary. Zinc has been known to play a pivotal role in the normal progression of the cell cycle for 50 years.[2] However, more recently, literature has shown zinc transporters to be involved in the development of epithelial-mesenchymal transition (EMT).[3, 4] EMT is hijacked by cancer cells to allow metastasis; therefore, it is hypothesised that blocking Zrt-/Irt-like protein (ZIP) transporters could prevent metastasis development.

This rapid review searched four independent databases (EMBASE, MedLine, Scopus, and Web of Science) to identify papers focussed on ZIP transporters and metastasis. 709 articles were identified for screening, where 14 records were chosen for inclusion in this review. To verify these results, database-mining was subsequently carried out where independent clinical data were analysed and compared to this review's results.

Paper screening identified ZIP4, ZIP6, and ZIP10 as being implicated in various cancers and metastasis development. Inhibition of ZIP4 and ZIP6 was found to reduce the metastatic potential of cells and improve survival rates. Database-mining confirmed the results seen in this review for ZIP4 and ZIP6; however, clinical data failed to support results for ZIP10.

ZIP4 and ZIP6 are heavily implicated in metastasis development, but more detailed research is required to fully elucidate the role ZIP10 plays in metastasis. Further research is also required to determine how ZIP transporters can be targeted for metastasis. However, due to both ZIP4 and ZIP6 being heavily implicated in the metastatic cascade, there is no doubt that ZIP transporters can play a pivotal role in metastasis treatment in the future by blocking a component of this cascade.

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A rapid review of the clinical consequences of trace element contamination in parenteral nutrition solutions

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Parenteral nutrition (PN) is the practice of giving patients' required nutrients intravenously. Trace elements are vital for human body function despite being required in minuscule amounts.[1] They are commonly added to PN solutions and given to patients with conditions that affect their trace element levels. e.g. cancer or Crohn's disease.[2,3] These PN solutions often become contaminated, which can be very problematic for the patient and needs further exploring. This rapid review aimed to review and critically appraise the existing literature on how these PN solutions become contaminated and the effect this has on patients.

Five main databases were searched (EMBASE, Medline, Scopus, Web of Science and PubMed) using defined key terms. No limits or study design restrictions were used to try and gather as many relevant papers as possible. The exclusion criteria included non-English papers, conference abstracts and guidelines. The papers that were finally selected were assessed for risk of bias using the Critical Appraisal Skills Programme and Joanna Briggs Institute checklists.

After searching the databases 2,445 papers resulted and these results were narrowed down following the PRISMA flow diagram and those eligible for inclusion were selected. Eleven studies were included in this review. A table was formed to compare the characteristics of the included studies which included the study design, contaminants analysed and key findings.

The findings show that contaminants originate from various sources and many factors influence the extent of contamination. The solution used, packaging used and the way the PN solution is stored can significantly change trace element concentrations and should be considered by health care practitioners and manufacturers. Dosages should be individualised in patients and adjusted in relation to contamination levels. Manufacturers should be advised to label their products with the exact concentration of each trace element rather than the expected concentration.

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Analysis and comparison of ECG data recorded from human volunteers using standard gel electrodes and novel microneedle electrodes

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Electrocardiograms (ECGs) are tools used by clinicians to observe the activity of the heart. They are vital diagnostic and monitoring tools used daily in cardiology, but can be very challenging to interpret, especially if signals are noise-corrupted and ambiguous.[2-4] Consequently, obtaining high quality signals is extremely important to minimise diagnostic errors and, thus, patient morbidity. Microneedles pierce through the stratum corneum, the outer skin barrier that reduces electrical conductance, so microneedle electrodes may record higher fidelity signals than the current 'gold standard' gel electrodes and also avoid the use of conductive gel which can dehydrate over extended periods.[1] This project aimed to conduct a thorough analysis of previously acquired ECG signals collected using both gel and microneedle electrodes, in order to assess the clinical feasibility of using microneedle-based electrodes.

The previous study collected three 1-minute ECG signals, with a rest in between, from 10 healthy volunteers. The methods to compare and analyse this data can be broken down into two categories: quantitative signal-to-noise ratios (SNRs), and qualitative visual comparisons to compare what the SNRs represent practically. All signal processing and data handling was performed using MATLAB.

Results were relatively erratic, but overall showed only a 0.1dB difference in average SNRs. The overall average gel electrode SNR was 27.6dB (n=30), and 27.5dB (n=24) for microneedle electrodes (p value was

0.724 with anomalous data removed). There was no significant statistical difference between the SNRs, and no significant visual difference was observed.

These results were congruent with those calculated in existing literature.[5] Although microneedle electrodes do not show significant advantages in this data, they are clearly viable alternatives to gel electrodes, with patient morbidity due to diagnostic errors not being affected by gel or microneedle electrode type. Further work is warranted to improve the retention of microneedle electrodes within skin during the data acquisition period.

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A rapid review: Should NHS Wales provide increased investment to extended stability studies in biopharmaceuticals?

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Since biologics (biological drugs) derived from a biological source, emerged onto the drug market they have revolutionised chronic disease states transforming their treatment and management. When biologics are licenced, pharmaceutical companies do not carry out extended stability studies. Extended stability data shows how the biopharmaceutical will perform under 'in-use' conditions (once reconstituted and/or diluted), which is crucial to Pharmacists and other Healthcare Professionals. For Summary of Product Characteristics (SmPC) shelf-lives to be extended, robust, valid data must be in the literature to support the claim of extended stability.

This rapid review aimed to identify biosimilars (which contain a version of the pre-authorised originator biologic) of Trastuzumab, Rituximab and Infliximab to investigate whether extended stability studies had been conducted, identify consistencies in methodologies employed, and evaluate whether NHS Wales could carry out their own in-house extended stability studies. Biosimilars are safe and effective in patients and with increased extended stability data, they could be used in place of more expensive originator biologics.

Embase, Medline and Scopus were systematically screened for primary papers that investigated the extended stability of UK licenced biosimilars. Following a 12-step duplicate removal process, exclusion criteria was applied to 3,606 papers resulting in 10 for critical appraisal. A PRISMA flow chart methodology was adopted in this review.

The literature review found extended stability of biosimilars for periods between 7-90 days. The methodologies used in the studies were compared against NHS guidelines for validity of results.[1] Importantly, these methodologies can be carried out by in-house laboratories for NHS Wales.

This review recommends NHS Wales should increase investment into extended stability studies of biopharmaceuticals. Purchase of these biosimilars is cheaper and through extended stability testing, NHS Wales can be reassured they are stable and effective over extended periods of time potentially allowing for advanced preparation and reduced wastage.

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How can inappropriate prescribing of sodium valproate be reduced?

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Sodium valproate is a drug used to treat epilepsy, mania and migraines.[1] Due to its teratogenic properties, its use is restricted in women of childbearing age.[2] A review has highlighted that many women of childbearing age are still inappropriately prescribed sodium valproate and calls for more measures to be introduced to prevent this.[3] This rapid review aims to evaluate the current scope of sodium valproate prescribing in Wales, identify measures other countries are using to reduce inappropriate prescribing of valproate and decide which measures can be implemented in Wales.

The databases EMBASE and Medline were searched, and the retrieved studies were screened against pre-determined inclusion and exclusion criteria, following the process set out in the PRISMA flow diagram.[4] Welsh prescribing data was obtained from the Welsh Analytical Prescribing Support Unit.

A total of 8 studies were included in this rapid review. The search identified two types of risk management measures used among 9 different countries. They can be split into educational measures, involving the distribution of teratogenic risk information to prescribers and patients and non-educational measures including implementing pregnancy prevention programmes and yearly meetings with specialists to assess treatment.

Educational measures had a limited effect at reducing inappropriate prescribing, whereas the non-educational measures have been effective. Further research is required to identify the reasons for these findings. Updated guidance for Wales should include the requirement of a pregnancy prevention programme, annual meetings with specialists and should ensure pharmacists are involved more in the information of risks to patients who are prescribed sodium valproate for the first time. New guidance should include more specific recommendations for patients with complex cases, such as women with intellectual disability.

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A rapid review of the development of 3D skin cancer models – characterising melanoma progression and invasion

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Melanoma, while being the rarest type of skin cancer it appears to be the most fatal due to the high risk of metastasizing and resisting treatments. One of the biggest struggles with melanoma treatments is the decreased reproducibility rate between results observed in animal models and human patients.[1] This grows the requirement for the development of more accurate human melanoma models. Current research on melanoma models focuses on 2D monocultures, 3D co-cultures or animal models.

To review the current status of representative models three databases were used; EMBASE, Medline and Scopus to find literature evidence. A set of pre-determined inclusion and exclusion criteria were set to identify the eligible studies for analysis .The studies were subjected to quality assessment using the CASP checklist and a customised checklist to exclude the unrelated papers. Data were then extracted and summarised in a table.

Out of 154 records initially identified, 13 papers met the inclusion criteria. Models with viable fibroblasts are generally thought to better mimic the in-vivo situation compared with the models with no fibroblasts, as many melanoma cell lines do not grow in their absence. The use of animal-derived products such as collagen can be avoided by using de-epidermised-dermis. Human skin cells can secrete their own physiological components of ECM and BM.[2]

This rapid review highlights the importance of including skin cells and basement membrane in melanoma models; describes the invasive properties of different melanoma cell lines and systematically compares the dermal matrices used in models.[3] Moreover; this project portrays the advantages and disadvantages of the different types of 3D melanoma models. Even though findings suggest that the most representative model is one that encompasses fibroblasts, keratinocytes and basement membrane into a de-epidermised dermis, further research is needed to investigate the optimal model that can recapitulate the complex melanoma architecture.

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

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

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

This review contains a total of 17 papers as a result of the screening process. Overall, multiple studies suggested biofilm production to be greater at higher temperatures and at prolonged incubation periods. Furthermore, strain variation appeared to have a great effect on the ability to form biofilms in both single and mixed species biofilms. Three studies focusing on potential management strategies showed a level of effectiveness including methods such as enzyme use, bacteriophage P100, nisin and neutral electrolysed water as a combination treatment.

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

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A rapid review of the development and potential of RAMBAs as therapeutics

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Retinoic acid (RA) plays an important role in the regulation of many essential biological functions and has been used in many clinical settings.[1] Due to adverse events and the development of RA resistance[2], retinoic acid metabolism blocking agents (RAMBAs) were investigated as an alternative or a complementary treatment of RA and RA derivatives. This review aimed to identify the current progress and applications of RAMBAs and predict the potential of RAMBAs as therapeutics.

A robust search strategy was employed on databases Web of Science, Scopus and PubMed to gather the most optimal literature for this review. Published papers were reviewed and selected based on a set of eligibility criteria with the use of the PRISMA flow diagram. Eligible studies were then taken forward for data extraction and analysis.

Of the 362 publications initially identified, 13 papers and 16 RAMBAs were included in this systematic rapid review. A variety of chemical structures and a wide range of IC_{50} values were obtained. However, promising results and consistency in properties of RAMBAs were demonstrated in various *in vitro* and *in vivo* assays and clinical trials, including anti-proliferative, apoptotic and anti-tumoural effects. Increase in CYP26A1 expression and RA plasma level were demonstrated in *in vitro* and *in vivo* assays. This confirms the accumulation of RA and the known mechanism of action of RAMBAs, which is one of the key properties to overcome RA resistance in clinical settings.

Based on the results obtained, further investigation is required to look into the structure-activity relationships of CYP26A1 and RAMBAs to enhance the potency and efficacy of RAMBAs. Overall, RAMBAs should be further developed based on the current available conventional treatments, specific to a disease. This way they will represent a valuable investment in the pharmaceutical industry and will have a prominent role in the near future.

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Can the high dose IV iron treatment regime be improved? A retrospective study, investigating the HDLF approach to IV iron treatment in Non-Haemodialysis Iron-Deficient Chronic Kidney Disease patients.

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Iron deficiency anaemia (IDA) is the most common nutritional deficiency worldwide. It is strongly linked with Chronic Kidney Disease (CKD) where most patients in Stage G4- G5 CKD will present with IDA. It adversely affects patients' quality of life and is associated with an increased mortality rate. The condition originates from an imbalance of iron intake and iron losses. Iron is an essential component of erythropoiesis, and erythropoiesis functions ineffectively during an iron-deficient state. If iron deficiency remains uncorrected, anaemia will ensue. Current guidance recommends parenteral iron treatment to correct iron levels in severe IDA patients. Latest guidance recommends intravenous (IV) iron by either the High Dose Low-Frequency (HDLF) regime or the Low Dose High-Frequency regime (LDHF). Erythropoiesis Stimulating Agents (ESA's) can also be offered to treat anaemia. This project aimed to analyse the HDLF approach towards iron treatment in IDA non-haemodialysis CKD patients and predict a dosing strategy that enables iron correction with a single or minimum infusion.

It is a retrospective data analysis study of 317 non-haemodialysis CKD patients from South West Wales Renal Unit. The data analysis comprised investigating patient characteristics, baseline blood results, IV iron dosages and ESA doses.

A strong relationship was established between a decrease in haemoglobin (Hb) response and declining estimated glomerular filtration rate (eGFR) [R^2=0.9651][p=0.0078]. This result gave rise to the idea of tailoring future IV iron doses based on patient eGFR at baseline, a method that has not been explored hither to.

This study led to discovering a potentially novel method of calculating future IV iron doses based on baseline eGFR values. Future investigations may ascertain this project's findings. It could lead to the development and optimisation of HDLF iron regime, benefiting IDA CKD sufferers.

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The impact of the All Wales COPD Management and Prescribing Guideline on inhaler prescribing across primary care in Wales

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Chronic Obstructive Pulmonary Disease (COPD) is an irreversible airway disease characterised by airway obstruction that effects over 76,000 people in Wales.[1, 2] In the past, prescribers would refer to their local health board guidelines for the management of COPD, resulting in seven slightly different guidelines across Wales. The All Wales COPD Management and Prescribing Guideline was introduced in May 2019 and aims to recommend the most up to date treatment pathways and to reduce inhaler prescribing variation.[3] This study aims to identify whether this guideline has influenced COPD inhaler prescribing habits across Wales.

The primary data source analysed was that of CASPA (Comparative Analysis System for Prescribing Audit) data which is a record of all primary care dispensed prescriptions. The inhaler classes analysed were Short Acting Muscarinic Antagonists (SAMA), Long-Acting Muscarinic Antagonists (LAMA), Long Acting Beta Agonists (LABA), LABA/LAMA, Inhaled Corticosteroid (ICS)/LABA and triple therapy (ICS/LABA/LAMA) from April 2018 to February 2020.[4]

The prescribing of LABA/LAMA and triple therapy inhalers continued to increase with no further increased rate in prescribing after the guideline introduction. Prescribing of the SAMA and LAMA classes continued to decrease without a further decrease in prescribing post guideline introduction. The LABA class was the only class where a significant decrease in prescribing occurred after the guideline. The overall ICS/LABA prescribing continued to decrease after the guideline introduction. Within this class, the Relvar Ellipta 92/22mcg and Fobumix Easyhaler 320/9mcg were the only two inhalers that are pictured on the guideline where prescribing significantly increased after its introduction.

The majority of inhaler prescribing trends did not change following publication of the All Wales COPD guideline, the trends continuing on the same trajectory throughout the analysis period. This suggests that publication of the guideline did not significantly change prescribing habits, rather it reinforced appropriate prescribing practice that fed into development of the guideline.

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A rapid review investigating the effect of Src kinase inhibition on endocrine therapy response of ER+ breast cancer models

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De novo and acquired resistance to endocrine therapies are persistent clinical challenges restricting success of breast cancer treatment[1]. Consequently, strategies to enhance endocrine therapy response or circumvent resistance are imperative. The non-receptor tyrosine kinase, Src, is involved in regulating various signalling pathways that control a plethora of cell functions and oncogenic characteristics[2]. Increased Src activity has been observed in breast cancer where it can regulate oestrogen receptor (ER) signalling, making Src an attractive anticancer target for these tumours[2]. This review investigated the effect of Src kinase inhibition on endocrine therapy response in ER+ breast cancer models, in addition to evaluating whether Src inhibition can enhance endocrine response in sensitive models or circumvent endocrine resistance.

Literature searches were conducted across five databases, investigating publications between 2015 and 2020. Sources were assessed against predetermined inclusion criteria, summarised per the PICO framework[3]. A PRISMA flow diagram was adopted for exclusion[4]. Quality and bias risk were assessed using an adapted CASP checklist. Relevant information was extracted from included sources and recorded in standardised tables.

Of the 243 sources initially identified, a final list of eight papers were included in this review after applying exclusion criteria. These studies represented preclinical in vitro, and in vivo data, and a clinical trial. Outcomes of preclinical experiments focused on growth, viability, and tumour volume. Outcomes of the clinical study focused on clinical benefit rate, progression-free survival, and osteopenia status. Data from included studies suggested Src inhibition resulted in enhanced sensitivity to endocrine agents compared to endocrine monotherapy, in both the endocrine-sensitive and endocrine-resistant context, across in vitro and in vivo experiments.

Overall studies suggest combining Src inhibition alongside endocrine therapy may represent a useful therapeutic strategy for ER+ breast cancer patients, particularly in selective patient subgroups, providing rationale for further research and hope for breast cancer therapy optimisation.

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Erythropoiesis Stimulating Agent (ESA) therapy in haemodialysis clinical practice: converting patients from Eprex to Mircera when treating anaemia of Chronic Kidney Disease (ACKD)

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Three million people in the UK suffer from Chronic Kidney Disease (CKD),[1] and anaemia is twice as likely in this patient group.[2] Erythropoiesis Stimulating Agents (ESA) are the current treatment of anaemia in CKD (ACKD).[3] Due to their costly nature, the ability to switch between ESA according to cost-effectiveness is of interest. In a longitudinal retrospective study, Eprex (Epoetin alfa), a short-acting ESA, was switched to Mircera (methoxy polyethylene glycol-epoetin beta), a long-acting ESA. The aim includes analysing the safety and efficacy of switching, determined by the maintenance of stable, in-range Hb (100-120g/L) in patients suffering from ACKD on haemodialysis (HD). A Dose Conversion Ratio (DCR) will be calculated and compared against current literature (1mcg:200IU).[4]

Patients with ACKD on HD (n= 142) in South West Wales (SWW) were analysed over 13 months from Baseline (Month -3 to -1, Eprex) to Evaluation (Months 1-9, Mircera), pre-and post- switch (Month 0). Sub-group analysis

included: Hb ranges, administration frequencies, cost, DCR (= Mean Monthly Dose (MMD) Baseline / MMD Evaluation). Statistical analysis of data was carried out in SPSS, figures were constructed in EXCEL.

MMD of Eprex (45143IU) and Mircera (181mcg) concluded a population DCR (Mircera / Eprex) of 1mcg:249IU. The majority of patients stayed within the Hb range at Baseline and Evaluation (66%, 64% respectively), mean Hb was 109g/L throughout. The mean monthly number of injections reduced from 11 (Eprex) to 1 (Mircera). Monthly Mircera administration required lower ESA doses to maintain stable Hb vs Fortnightly.

The established DCR displayed greater bioequivalence of Mircera vs current literature[4] and a ~25% decrease in annual patient cost. Stable, in-range Hb was maintained by both drugs. Lower monthly administrations of Mircera vs Eprex would benefit the cost-effectiveness of ACKD treatment. Study findings fill the current void in guidelines, forming reliable evidence from clinical-based data.

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Investigating the Therapeutic Potential of Inhibiting Histone Deacetylase Activity to Treat Huntington's Disease

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Huntington's Disease (HD) is an inherited neurodegenerative disorder. Symptoms worsen over time, and the period from their initial onset to patient death is on average 15-20 years. Although medicines exist to reduce the symptoms of Huntington's, there is currently no licenced therapeutic treatment available.[1-3] HDAC inhibitors have demonstrated a degree of success in ameliorating Huntington's Disease symptoms in different HD models. The aim of this review is to evaluate the potential of a limited number of non-selective and selective HDAC inhibitor (HDACi) candidates for the treatment of Huntington's disease. As such, I conducted a critical appraisal of seven studies which involved the use of HDACis on mouse and Drosophila HD models, assessing the quality of the evidence presented from each study. The papers selected investigated the link between a decrease in histone deacetylase activity and the amelioration of Huntington's disease symptoms. Papers that involved the use of HDACis that exhibited therapeutic mechanisms other than inhibiting histone deacetylase activity were excluded from selection. I included papers investigating the effects of a decrease of histone deacetylase activity on Huntington's disease via the use of gene knock out methods. After a careful analysis of the key results from each paper, I concluded that although the selective HDACi treatments considered demonstrated a marked improvement in disease outcomes across the models used, more needs to be understood about how they work for them to surpass other more targeted therapies in the search for an effective treatment for Huntington's disease. More needs to be understood about how mutant huntingtin exerts its pathogenic effects before increasing gene transcription is considered the preferred therapeutic target. Currently, more direct approaches (e.g., directly targeting the production of the mutant huntingtin protein) are at the head of HD research.

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How does anthracycline chemotherapy affect Ca^{2+} signalling in the cardiac sarcoplasmic reticulum to bring about cardiotoxic effects?

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Anthracyclines are used in chemotherapy to treat various forms of cancer, however their use is limited due to the phenomenon of dose-dependent cardiotoxicity.[1] Anthracyclines bring about cardiotoxic effects by many mechanisms including directly binding to calcium regulatory proteins in the cardiac sarcoplasmic reticulum (SR). These proteins include the calcium release channel (or cardiac ryanodine receptor, RyR2), the calcium reuptake ATPase pump (SERCA2a) and the calcium buffering protein, calsequestrin (CSQ2).[2] Binding causes disruptions to normal calcium handling, leading to cardiac remodelling. The aim of this project was to collate and evaluate current literature available on the possible mechanisms behind anthracycline-induced cardiotoxicity.

Having identified search terms based on the key concepts in my project title, I used three databases for my literature search (Scopus, Medline and Embase). Articles were screened for eligibility against inclusion and exclusion criteria, resulting in fifteen peer-reviewed articles from which data were extracted.

Anthracyclines cause cardiac dysfunction by changing the expression and function of SR proteins. Expression of RyR2 or SERCA2a increased or decreased depending on the anthracycline used, causing imbalances in calcium regulation. Functional changes were as a result of either direct binding to the protein, or by virtue of thiol oxidation caused by anthracycline-induced reactive oxygen species.[3] Effects on RyR2 were biphasic in nature, with lower doses causing channel activation and higher doses inhibiting the channel. These changes led to either increased or decreased cytoplasmic calcium levels.

As calcium drives cardiac muscle contraction, increased calcium would explain arrhythmogenesis, more specifically tachycardia. Reductions in calcium would explain inadequate cardiac contractility, contributing to heart failure. However, details regarding the underlying mechanisms of anthracycline-mediated cardiotoxicity still remain unclear, and require further investigation.

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Evaluation of Ex Vivo and In Vitro Models of Fungal Keratitis: A Rapid Systematic Literature Review

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Filamentous fungal keratitis caused by *Aspergillus spp*. and *Fusarium spp*. are a severe corneal infection that may lead to vision loss if treatment is unsuccessful.[1] While topical natamycin has been the unlicensed first-line treatment for years in the UK, there is interest in improving the bioavailability by exploiting nanotechnology as ocular drug delivery.[2] This systematic review aimed to evaluate *ex vivo* and *in vitro* models of fungal keratitis which can be used to assess drug delivery of antifungals to the cornea**.**

Three different database resources were used to find the literature on the *ex vivo* and *in vitro* models of fungal keratitis; PubMed, Web of Science, and SCOPUS. Inclusion and exclusion criteria were implemented towards publications for screening eligibility. All papers included were critically appraised and the relevant data extracted from the selected publications were analyzed.

16 publications were reviewed altogether; 8 papers for both *ex vivo* and *in vitro* models, respectively. This review mainly focused on the methodology and summarised it into the following parameters; type of models, fungal strains, inoculation or incubation procedure, incubation period, and assessment of the disease progression.

Rabbit and porcine corneas were determined to be good substitutes to human corneal models for e*x vivo* infection models and HCECs cell models are being the best models to represents the closest to clinical fungal keratitis for *in vitro* infection models. However, further studies need to be done on the drug corneal permeation in correlation with this paper to study the filamentous fungal keratitis treatment as a whole.

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Antimicrobial peptides: viable alternatives to antibiotics?

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The widespread antimicrobial resistance poses a challenge to global health, creating a pressing need for new antimicrobial agents. Antimicrobial peptides (AMPs) are a natural component of the innate immune and possess broad-spectrum activity. Their cationic properties and amphiphilicity drive their antibacterial mechanism. For this reason, they have been investigated as alternatives to antibiotics. However, knowledge is lacking regarding their potential for this role. This rapid review aims to investigate and analyse the potential of AMPs based on their clinical applications and to address the hypothesis of whether AMPs are viable alternatives as antibacterial agents.

The names of AMPs in clinical trials were compiled from the database, Data Repository of Antimicrobial Peptides (DRAMP) and supported by data from other systematic reviews. A specific search terms algorithm was used for the scoping process from EMBASE and Scopus conforming to the selection criteria. PRISMA flowchart displayed an overview of the scoping process. The finalised publications were critically appraised before being analysed.

This review observed the tremendous growth of AMPs research area and discovered 41 AMPs assessed for various indications in clinical trials. The data from 32 publications was summarised into sections: mechanism of action, synergy activity, the resistance propensity of bacteria against AMPs, factors affecting their activity, comparison to conventional antibiotics and drug optimisation strategies.

From the susceptibility tests against various bacteria, the investigated AMPs showed promising antibacterial properties concentration and were prominent in other diseases categories. The findings support the hypothesis emphasising the exciting potential of AMPs as alternatives to antibiotics or use in combination therapy to treat bacterial infections. In conclusion, AMPs have huge potential as antibacterial entities, but a few fundamental issues such as their toxicity and tendency for pathogens to develop resistance against them, need to be overcome to guarantee they truly represent our attempts to overcome drug resistance.

A rapid systematic review of the effectiveness of the influenza vaccine in aged persons with COPD

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Persons aged 65 and over with Chronic Obstructive Pulmonary Disease (COPD) are an extremely vulnerable subgroup of the population. An aging immune system[1] in combination with long-term damage and inflammation to the airways[2] means that these patients are at a high risk of developing severe complications if they contract influenza. Not only can this lead to hospitalisation or mortality, but it also places a massive burden upon healthcare staff, costs, and facilities.[3] As influenza is a global public health issue that recurs annually, it is essential that aged persons with COPD are adequately protected.[4] The aim of this rapid review is to evaluate the effectiveness of the influenza vaccine in aged patients with COPD by assessing hospitalisation and mortality rates.

Literature searches were carried out in four databases: Embase, Emcare, Medline and Scopus. Identified literature was screened and subjected to predetermined inclusion and exclusion criteria to assess appropriateness for inclusion. All studies were assessed for quality and risk of bias. Six research papers underwent full-text analysis, data extraction, and variables were assessed.

Results showed that influenza vaccination was associated with a reduction in hospitalisations due to influenza, pneumonia, and COPD exacerbation. Vaccination also significantly reduced the risk for the occurrence of first hospitalisation due to acute coronary syndrome in aged COPD patients. Additionally, all-cause, COPD-related, pneumonia and influenza-related mortality were reduced in vaccinated groups.

Key findings suggest that influenza vaccination dose have a protective effect in COPD patients. However, due to the lack of research in this subgroup the extent of this protection cannot be determined. The limitations of this review include time restrictions and inexperience of the researcher. Further research into different types on influenza vaccine and the role of cumulative vaccination would be beneficial to ensure protection for aged persons with COPD.

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The safety and impact of non-specialist penicillin allergy de-labelling services: a rapid systematic review.

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A tenth of the UK population have a documented penicillin allergy.[1] It is believed that 90% of these do not have a true allergy or have grown out of their allergy[1]. Penicillin allergy labels are associated with poorer clinical outcomes and resistance due to use of inappropriate antibiotics. Due to a lack of clinical immunologists in Wales, it has been proposed that there is a market for a non-specialist de-labelling service to remove these inappropriate allergy labels.

Six databases were searched from 3/11/20 - 8/11/20. Exclusion criteria were set, and papers more than 20 years old, non-English language papers and conference papers were removed, as were papers which discussed research not associated with the impact and safety of non-specialist services. Remaining papers were critically appraised using checklists from the Joanna Briggs Institute[2] and the British Medical Journal,[3] and a narrative synthesis undertaken.

In total, 593 papers were identified and six were included in the review. It was found that a non-specialist penicillin allergy de-labelling service has been implemented successfully in all of the hospitals studied, with little complication. A variety of non-specialists, including pharmacists, were used in the different settings and with different team dynamics. Multiple de-labelling methods were studied, and all were deemed safe. The biggest benefit was that associated with cost-saving.

A non-specialist penicillin allergy de-labelling service appears to be feasible in Wales, in terms of safety and efficacy. However, cost savings associated with the service may not be sufficient to account for its widespread use: a service may have to be limited to high-risk patients where no other antibiotic alternatives can be used. It would also be helpful to have UK-based future research, including a study into the opinions of staff and patients prior to deciding on implementation of this beneficial service.

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Exploring the current knowledge and confidence of community pharmacists in the management of IBD patients in Wales

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Classed as Europe's second most prevalent chronic non-fatal disorder in 2008, inflammatory bowel disease (IBD) is an umbrella term used for three conditions: Crohn's disease (CD), ulcerative colitis (UC) and the less frequently acknowledged, microscopic colitis (MC).[1,2] Evidence shows healthcare professionals (HCPs) have limited knowledge of IBD, especially from the patient's perspective.[3] This pilot study aims to explore the current knowledge and confidence of community pharmacists working in Wales in the management of IBD patients in collaboration with Tillotts Pharma UK who will use these findings to develop educational materials to improve IBD knowledge.

A non-probability sample was recruited using purposive and snowball sampling whilst ensuring all participants were practicing community pharmacists in Wales. Through semi-structured interviews and questionnaires, qualitative and quantitative data were collected, respectively. Questionnaires were used to attain quantitative data from a larger pool of pharmacists whereas interviews enabled pharmacists to give more in-depth responses and raise topics of interest.

Six main themes were identified, supported by verbatim quotes and questionnaire results. These included: the impact of the COVID-19 pandemic, pharmacists' knowledge and management of IBD, education, rectal products and pharmacists' future role in IBD management. Pharmacists reported low levels of knowledge of IBD with no knowledge of MC. Pharmacist-led IBD management was limited due to time constraints and relied on patient self-management. However, pharmacists showed great interest in further education around IBD and increasing their role of educating IBD patients.

This small-scale study has identified pharmacist's limited knowledge of IBD and poor awareness of MC. Similarly to other HCPs, limited conversations with IBD patients and inadequate training around IBD has meant pharmacists lack understanding from the patients' perspective, leaving patients with inadequate guidance. With improved knowledge, there is potential for pharmacists to educate IBD patients, maximise adherence and improve patient outcomes in the future.

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The impact of the first wave of COVID-19 on antimicrobial prescribing patterns in Cwm Taf Morgannwg UHB

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Antibiotic discovery transformed the world, decreasing bacterial infection mortality rates globally.[1] However, the emergence of COVID-19 in December 2019 paralysed the world and changed societies forever, affecting everything from healthcare to education.[2] This study aimed to investigate the impact of COVID-19 on antibiotic prescribing in Cwm Taf Morgannwg UHB (CTMUHB).

The research method entailed extracting anonymous CASPA primary care antibiotic prescribing data for April-June (Q2) 2017-2020. Retrospective data analysis was conducted to explore how antibiotic prescribing before COVID-19 compared to antibiotic prescribing after the onset of COVID-19. Literature studies and other clinical sources e.g.) AWMSG and ICNARC reports were consulted as evidence for the trends identified.

The results showed a decrease in total antibiotic prescribing during the lockdown (Q2 2020) when compared to the same period in previous years. Amoxicillin displayed the most significant reduction (41%) between Q2 2019 and Q2 2020 ($P<0.05$). COVID-19 appeared to have little impact on antibiotics predominantly used for UTI's (trimethoprim and nitrofurantoin). This research also highlighted the higher antibiotic prescribing rate of CTMUHB compared to the rest of Wales, both before and after the onset of the pandemic. CTMUHB prescribed 10% more antibiotics in Q2 2019 (pre-COVID) and 11% more in Q2 2020 (during COVID) compared to the rest of Wales.

Overall, the study showed the effectiveness of the lockdown and social distancing on reducing infection transmission and subsequently, antibiotic prescribing. Although, these results are promising, the restrictions are unfortunately not sustainable. Additionally, interventions are needed to reduce antibiotic prescribing in CTMUHB. Further investigation is required to see whether the second COVID-19 wave had the same impact on antibiotic prescribing and how the recommendations made in this study can be implemented to benefit patients and slow antibiotic resistance.

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A review of the management and delivery of palliative care, through the NHS 111 Wales Clinical Support Hub, within Aneurin Bevan University Health Board

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The demand for palliative care is increasing[1] and adapting healthcare systems[2] to address patient needs is vital. NHS 111 Wales provides care, medications and advice outside of normal working hours. Calls requiring clinical input are referred to the Clinical Support Hub. Despite its value, where NHS 111 Wales is accessed to support palliative patients, it may suggest an oversight in planned care. This study aims to identify the volume and nature of palliative care calls referred to the Clinical Support Hub, within Aneurin Bevan University Health Board (ABUHB).

1902 call logs were received and coded based on their Information Outcome codes (IOC). All calls were descriptively analysed in SPSS, identifying peak call times, OOH prescribing rate and IOC frequency. Inductive thematic analysis, of a stratified sample of 10% of the case summaries identified call themes.

Palliative care patients called more frequently on weekends (9.6 calls/day) than weekdays (3.4 calls/day), with calls peaking at 8pm every weekday and 10-11am on weekends. Most calls (86%) were resolved without prescriptions. Few contacts had a Specific Patient Note (SPN) (23%) a marker of planned care. ‘Palliative Care’, ‘Self Care’ and ‘Advise Contact GP’ were the most common IOCs. Of codes comprising <5% of calls, ‘Death’, ‘Refer to Other HCP’ and ‘Refer to Secondary Care’ were most common. ‘Medicines Administration’ was the most common subtheme (35%), with 8.9% requiring prescriber input.

The lack of OOH prescribing suggests anticipatory prescribing within Wales[3] is well utilised. Promotion of schemes (e.g., CARiAD package[4]) improving medicine administration access would reduce patient wait times and impact on NHS 111 Wales. The 8pm call peak coincides with district nurse services closing. Ensuring enough clinical staff are available at peak times will improve patient outcomes. Expanding non-clinical carers’ roles would make OOH care more accessible, reducing NHS 111 Wales’ pressures.

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Secondary Analysis of the Synergistic Bactericidal Activity of Pomegranate Rind Extract and Zn (II) Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Methicillin-Sensitive *Staphylococcus aureus* (MSSA)

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Research shows that *Punica granatum L*. has antibacterial activity against Gram-positive and Gram-negative bacteria[1]. This research aims to assess if synergy is present between Pomegranate Rind Extract (PRE) with Zinc Sulphate ($ZnSO_4$) to demonstrate bactericidal activity against two strains of Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Methicillin-Sensitive *Staphylococcus aureus* (MSSA) *in vitro*.

This research is a secondary analysis of bacterial suspension tests completed by previous students, which assess the efficacy of an antimicrobial in inactivating test microorganisms in suspension within a specified contact time[2]. ANOVA analysis and unpaired t-tests tests were performed on the resulting raw data from these experiments to explore differences between the efficacy of PRE and Zn (II) alone and in combination to determine if synergistic bactericidal activity exists.

Global ANOVA tests against MRSA demonstrated that there is limited bactericidal activity in all test samples until 20 minutes contact time. At 20 minutes, there is synergy between PRE 1mg/mL+ Zn (II) 0.5M showing a log reduction value of 4.41 ($p<0.0001$). In contrast to this, Zn (II) 0.5M and 1M alone achieve maximum possible kill at one hour, around 6 log reduction, which is maintained on the addition of PRE. Minimal bactericidal activity is observed against MSSA, with global PRE/Zn (II) showing a log reduction of 0.267 at 10 minutes contact time ($p<0.05$).

This research shows that synergy exists between PRE and Zn (II) against *Staphylococcus aureus*. Surprisingly, despite MRSA's notorious antibiotic resistance, synergistic bactericidal activity is significantly greater against MRSA than MSSA. With respect to MRSA, the data in this research displays inconsistencies between student data sets so further research is needed to support synergistic bactericidal activity. Additional research is also needed for MSSA due to only having data available for a contact time of 10 minutes, which shows minimal bactericidal activity.

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Reducing Incidents Stemming from Known Antibiotic Allergy (RISK – Antibiotic Allergy)

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Many drug errors occur globally surrounding the administration of antibiotics to those who are allergic to them[1], avoiding such incidents is important for patient safety. This study aimed to understand this issue from a Welsh perspective, and to identify and assess methods used to avoid these incidents by undertaking a rapid review.

A rapid review was undertaken using PRISMA guidelines.[2] Primary research published, in English, in the last 20 years was identified from seven databases. Research not relating to incidents or errors stemming from administration of an antibiotic to an allergic patient was excluded. Eligible papers were quality appraised and a narrative synthesis undertaken. In addition, anonymised data from Welsh Health Boards relating to incidents over the past 5 years were analysed to provide a descriptive overview. Ethics approval was not needed.

Data analysis of 240 patient safety reports of antibiotic allergy incidents revealed that 84.6% of incidents occurred where the allergy incident was that of a previously known allergy. Most (81.3%) incidents related to penicillins, with tazocin, co-amoxiclav, amoxicillin and flucloxacillin jointly accounting for 75%. The rapid review returned 1140 initial results. Removal of duplicates and ineligible papers led to 9 papers being used to draw conclusions following their critical appraisal. Rapid review revealed methods from the use of computerised physician order entry systems, the increase in responsibility of pharmacists, separate storage of penicillin-containing antibiotics to biometric/barcoded patient information.

Further research must be carried out to evaluate the impact of increasing the responsibility of pharmacists, or the creation of dedicated ward/clinical pharmacists for the bureaucracy of antibiotic allergies, a method solicited by multiple papers found through rapid review. It is also suggested that there is a lack of knowledge surrounding antibiotic allergy, which must be remedied with increased education and signposting.

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Trace Element Contamination of Parenteral Nutrition

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Parenteral nutrition (PN) is the intravenous administration of macro- and micronutrients in patients who are unable to eat or absorb enough food.[1] In recent years, the use of PN has progressively increased particularly in the US.[2] Trace elements (TEs) are either essential or non-essential for humans, however both groups cause toxicity at high levels.[3] It has been established that PN solutions can be ubiquitously contaminated by TEs. The aim of this project was to identify which TEs cause contamination of PN since 1995, if that TE is still a clinical issue and to give potential reasons for TE contamination.

Four databases PubMed, Embase, Web of Science and Scopus were used to search the literature and papers were extracted into EndNote X9. Studies were screened for eligibility against inclusion and exclusion criteria and a PRISMA flow diagram was followed. All papers were critically appraised using a CASP checklist.

13 papers met the eligibility criteria for this review. This review summarised: the study design, TE tested, analytical methods and results from each study. The following TEs were found to cause contamination since 1995: chromium, aluminium, zinc, copper, arsenic, boron, tin, strontium, vanadium, selenium, manganese and barium.

Currently, contamination by chromium, aluminium, arsenic, vanadium, manganese and barium are clinically significant and can potentially lead to toxicity. Contamination by all other TEs found were deemed clinically insignificant. Potential reasons for contamination are manufacturing process, materials such as glass and rubber stoppers, and PN products such as calcium gluconate and potassium chloride. A limitation of this review was that 8 of the 13 papers used were published from 1998-2007. Therefore, further research is needed to in the TEs that have been shown to cause harmful contamination.

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A rapid review on the efficacy and safety of NS2B/NS3 protease inhibitors for the treatment of dengue and zika virus infections.

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The global incidence of dengue virus (DENV) cases has been increasing at a rate of 400% over the last 13 years, and about half of the world's population is now at risk. [1] Due to the epidemics and teratogenic potential, in 2016, the World Health Organisation included Zika virus (ZIKV) as a Public Health Emergency of International Concern. [2] There is currently no therapy available for the treatment of DENV and ZIKV infections and to mitigate the geographical expansion and manage outbreaks, it is necessary to find specific treatments that can be implemented across affected communities. [3] This study aims to review the literature on the developed NS2B/NS3 protease inhibitors of ZIKV and/or DENV and assess their clinical translational potential for the treatment of these viral infections.

A literature search was conducted using three databases, Scopus, Medline, and Embase, to find journal articles reporting *in vitro* and/or preclinical data of DENV and ZIKV NS2B/NS3 protease inhibitors. Articles were screened against the predetermined criteria and the included studies were further assessed using a quality assessment checklist. Data from the relevant studies was extracted and analysed.

In total, 19 promising compounds were identified from the selected articles, all of which were shown to inhibit NS2B/NS3 protease activity to some degree in biochemical assays and inhibit DENV and/or ZIKV replication in cell-based assays. Some inhibitors were also characterised for their in vivo efficacy, enzymatic selectivity, synergistic activity, susceptibility to develop drug resistance, broad-spectrum coverage, and pharmacokinetic properties.

The findings suggest that NS2B/NS3 protease inhibition may be a feasible antiviral approach to combat DENV and ZIKV infections. The inhibitors identified in this study can act as lead compounds and could guide the development of more potent agents. However, these inhibitors will need to undergo further preclinical tests before they can be considered for clinical use.

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What is the optimal approach of low frequency high dosing of intravenous iron in renal patients not receiving in-centre haemodialysis? A Quantitative Data Analysis

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A common manifestation of chronic kidney disease (CKD) is iron deficiency anaemia.[1] A high dose low frequency (HDLF) intravenous iron approach is recommended as treatment in non-haemodialysis patients and defined as a minimum of 500mg iron given in a maximum of 2 infusions.[2] HDLF is a desirable approach as it is more likely to improve iron levels in a single infusion, allowing patients to have less frequent hospital visits and reduced requirement for needle insertions.[1] However, no exact guidance is specified on precise dosing through HDLF to achieve and maintain sufficient iron stores. The current HDLF approach requires considerable improvement as 60% of patients in the study experienced a relapse after their first HDLF intravenous iron dose. Hence, this quantitative data analysis aims to identify optimal approaches to intravenous iron dosing through HDLF to assist clinicians in future iron dose decision making.

Microsoft Excel© was used to carry out statistical analysis of data set provided by South West Wales Renal Unit, using formulas and graphs to identify correlations and findings.

The analysis identified a highly significant relationship between eGFR (Estimated Glomerular Filtrate) levels and patient iron response, with lower eGFR levels being associated with a poorer response to iron therapy. It also recognised the role of serum ferritin potentially being more inclined as an inflammatory biomarker in renal patients over indicators of iron stores as it usually would be under normal circumstances which reduces the reliability of using serum ferritin in clinical practice as clear indication of patient's iron stores.

Overall, it is hopeful that eGFR can be used as a consideration factor in iron dose decision making in the future for improvement of iron therapy to allow higher proportion of patients achieving and maintaining sufficient iron levels for a prolonged period of time. However, further research would be required to examine the efficacy of this relationship.

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Pharmacist Independent Prescribers scope of practice and the Designated Prescribing Practitioner: Secondary qualitative analysis to develop a Questionnaire.

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Pharmacists gained the ability to prescribe independently, without other healthcare practitioner (HCP) involvement in 2007[1]; provided they complete a postgraduate independent prescribing course. During this course, aspiring Pharmacist Independent Prescribers (PIPs) define an area of medicinal practice, known as their 'scope', within which they are competent to prescribe. A prescribers survey report published by the General Pharmaceutical Council (GPHC) concluded *"further clarity on how to... expand one's scope of prescribing practice was needed"*.[2] Thus an aim of this study is to investigate how PIPs are currently expanding their scope of practice.

To enrol onto the course, the aspiring PIP must find a Designated Supervising Medical Practitioner or DSMP to tutor and supervise them in practice. They must spend 90 hours of supervised learning in practice, as set out by the GPHC.[3] It is not known how these 90 hours are spent, what other HCPs are involved and what skills they impart. One aim of this study is to investigate this trifecta.

To meet the aims, secondary qualitative analysis of anonymised transcripts from previous interviews, literature and guidelines were undertaken. This was combined with questionnaire design literature[4] to produce a first draft questionnaire that will be sent out to PIPs across Wales. This was then further refined through supervisor input, piloting and ethics recommendations. Finally, this was converted to an online format for distribution.

The end result was a refined and tested tool that when distributed should answer our aims; it has been given the best chance of doing so through continuous re-drafting after each input. In conclusion, whilst the questionnaire rollout has been delayed, it has been set up to have a good response rate through this delay. It is also understandable to the target audience, as verified through the piloting step, therefore it will be useful to yield a picture of opinions of pharmacists across Wales.

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Waging the war against antimicrobial resistance: the current challenges and outlook for Antimicrobial Peptides in their quest to clinical success

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Overreliance on antibiotics, coupled with the lack of development of new antibacterial agents, with novel mechanisms of action, accelerated the global spread of multidrug resistant bacteria. AMPs are a class of short cationic peptides that showed to inhibit bacterial growth of a range of gram-positive and gram-negative bacteria, *in vitro* and *in vivo*. The significant investment into evaluating AMPs as novel anti-infectives, is not translated in a high number of FDA approved peptides. This review aimed to assess the rigor of pre-clinical evaluation of AMPs currently in trials and draw conclusions for further therapeutic avenues for AMPs.

Three online databases, Web of Science, PubMed and EMBASE, were consulted to identify pre-clinical papers pertaining to each AMP. Published papers were subsequently subjected to exclusion and inclusion criteria and a qualitative appraisal. A total of 52 eligible studies were brought forward, for data extraction and analysis.

Although 90% of AMPs were evaluated *in vitro*, their efficacy was tested against a narrow range of bacterial species. The AMPs analysed *in vivo*, against conventional treatment, established a trend of AMPs failing as therapeutics in animal models. The unfavourable toxic profile of AMPs, reflected in the narrow therapeutic index, was an important finding from this study. Mechanistic studies provided evidence for the membrane disruption, as well as the non-membranolytic mechanism of AMPs. A secondary finding was an immunomodulatory effect, exerted by 20% of AMPs. The dual mechanism of AMPs could contribute to the low propensity for resistance, demonstrated in resistance assays. Synergy studies illustrated a promising therapeutic avenue for AMP-Antibiotic combination treatment, perhaps due to their complementary mechanisms of action.

The antibacterial properties of AMPs could be optimised through developing structure-function guidelines, based on their sequences, to create rationally designed AMPs. This may pave the way for a higher proportion on AMPs reaching the clinic.

Can the frequency of haemodialysis be temporarily reduced in selected patients using careful risk-stratification during COVID-19?

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Chronic Kidney Disease (CKD) is defined by abnormal kidney function and/or structure and treatments include regular haemodialysis (HD).[1] COVID-19 enforced a change in practice for the South West Wales (SWW) Renal Service due to unprecedented demands for kidney dialysis fluids and patient management. To reduce COVID-19 exposure to highly vulnerable dialysis patients the service decided to reduce the frequency of haemodialysis in carefully selected patients to twice a week over 9 weeks. Dialysis patients are more likely to experience hyperkalaemia[2] therefore, sodium zirconium cyclosilicate (Lokelma), a potassium-binding drug was prescribed to some patients. The main aim of this study was to ascertain whether haemodialysis frequency can be safely reduced temporarily during a COVID-19 outbreak following careful risk-stratification.

The renal team at Morriston Hospital initiated the accumulation of data from 85 patients attending the dialysis unit in Carmarthen. Pre-dialysis serum potassium and bicarbonate levels were recorded regularly in all patients. A survey was then issued to twice-weekly HD patients to explore their views on the experience.

An overall increase in mean pre-dialysis potassium occurred in patients during twice-weekly HD. However, all levels remained within the recommended range of 3.5-5.9mmol/L.[3] Additionally, only 3 patients who received Lokelma had a mean potassium level above 6.0mmol/L during the intervention. The mean pre-dialysis bicarbonate remained slightly lower (21.31mmol/L) than the safe range of 22-29mmol/L[4] in patients who did not receive Lokelma compared to the patients who did receive Lokelma (22.4mmol/L). The survey (n=40) responded that 60% felt no different and 90% did not feel more unwell on twice-weekly HD.

In this study, the clinical safety of twice-weekly HD was demonstrated over a short period only to accommodate the challenges of COVID-19. The data supports future research to explore if any long-term adverse effects are associated with reduced dialysis frequency.

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Investigating the prescribing of Asthma Medicines in Wales at the Primary Care Cluster level

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Asthma is a chronic, inflammatory disease of the airways characterised by shortness of breath, wheezing and tight chest. The prevalence of asthma in Wales is reported to be one of the highest in the world. There were 3,483 emergency hospital admissions in Wales as a result of asthma exacerbations in 2016/17.[1] The number of asthma deaths in Wales and England have increased by 33% in the last decade[2] and the majority of deaths were found to be avoidable. This project aims to identify potential inequalities in the prescribing of medicines to treat asthma in primary care clusters in Wales. Investigating prescribing data at a cluster level gives much more granularity than prescribing data on a local health board (LHB) level.

Asthma medicine prescribing data was received from (CASPA) database from All Wales Therapeutics and Toxicology Centre.

This project has generated a unique picture of the asthma medicine prescribing tendencies of primary care clusters in Wales. The most notable findings are similar to previous studies[3], which are overprescribing of short-acting beta-2-agonists (SABA) inhalers and under prescribing of inhaled corticosteroids (ICS). Furthermore, no clear relationship was found between primary care cluster, adherence to guidelines and deprivation.

The conflicting guidance given by BTS/SIGN and NICE makes it difficult for prescribers, especially in primary care, to know how asthma should be diagnosed and managed and this leads to prescribing inequality across primary care clusters. Therefore efforts need to be made to improve prescribing to ensure asthma patients receive appropriate care in all areas of Wales.

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Antileishmanial activity of natural products: A rapid systematic literature review

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Leishmaniasis is a disease, which is transmitted through the bite of a female sandfly. There are 3 main types of leishmania: cutaneous, visceral and mucocutaneous.[1] The most common one is cutaneous leishmaniasis, which causes skin lesions after being exposed. Visceral leishmaniasis affects the internal organs such as the spleen and the liver. Mucocutaneous leishmaniasis is the least common one however partial destruction of mucosal membrane can occur if left untreated.[1]

The most frequent key term used was “Leishmania and natural products and plants”. PubMed, Web of Science and Scopus were the 3 databases used to find data. After several stages of screening, 15 papers were used for the final critical review. Publications that did not seem relevant to the study were removed.

The results gathered suggested that some of the extracts had good potential to treat leishmaniasis. The IC_{50} values from the extracts suggested that certain extracts have good antileishmanial activity against the leishmania parasites, in particular the hexane extract of dipteryx alata, which showed an IC_{50} value of 0.08 µg/mL[2] against leishmania amazonensis.

After reviewing the publications, the use of natural products is vital for the treatment of leishmaniasis and more research needs to be done in this area to find a suitable treatment for leishmaniasis. The current treatments for leishmaniasis have harsh side effects and resistance has also been reported.

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A Rapid Review Assessing the Role of ZIP7 in Cancer and its Potential as a Cancer Treatment Target

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The zinc transporter, ZIP7, is critical for cytosolic zinc regulation which can induce cell growth.[1] Therefore, elevated ZIP7 has been associated with cancer progression. This rapid review attempts to collate the relevant literature surrounding the role of ZIP7 in cancer. The primary aim is to examine whether ZIP7 is involved in cancer pathology and therefore suggest whether ZIP7 could be a good cancer treatment target.

Initially, 844 publications were gathered from five online databases. After de-duplication, screening and eligibility checking, eleven papers remained to be appraised. The resulting literature was scrutinized using an appropriate critical appraisal checklist. Supplementary clinical database analysis was completed to clarify the reliability of the results.

The review found ZIP7 was significantly upregulated in breast, gastro-intestinal, lung, and cervical cancers. Furthermore, ZIP7 positively correlated with increased cell proliferation, migration, and invasion. Consistently, the results showed ZIP7 activated signalling molecules and pathways, whilst inhibited pro-apoptotic proteins. The clinical data analysis supports the review results, showing that ZIP7 was significantly upregulated in 14 different cancers.

ZIP7 is a key regulator of cytosolic zinc, which when free in the cytosol can activate a plethora of signalling pathways and molecules, inducing cell growth.[2] When ZIP7 is upregulated, it corresponds to increased cell proliferation, hence inhibition of ZIP7 can halt or prevent the aggressive growth of cancers. Currently, no drug treatments exist for ZIP7 and each proposed strategy have drawbacks, there is a lack of substantial primary *in vivo* data and the influence of ZIP7 in many cancers have yet to be investigated. So, more research in these areas is necessary to confirm the extent to which ZIP7 inhibition will be a successful cancer treatment approach.

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A comparison of activators of Gamma Delta T Cells: a rapid systematic literature review

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Gamma delta T cells are a subset of t cells capable of recognising and targeting cancer cells found in human blood.[1] They are activated via phosphoantigens binding to the transmembrane protein Butyrophillin 3A1.[2] These cells have shown prolific ability to perform in an immunotherapy role.[3] The objective of this review is to assess the suitably and effectiveness of these compounds and any additional study is required.

The search terms of “Prodrug, Cancer and T cell” have been used to search publications from SCOPUS and PUBMED to find papers related to these search terms. Only papers included within the last 20 years have been included to provide the most up to date information. The final papers have been critically aprased based on a qualitative checklist prior to inclusion.

The results have suggested phosphoantigen prodrugs with an ester motif show the most potent activation showing good metabolism, binding and Log P values. Additionally this study has shown the importance of insulating the Phosphate group from unspecific esterases such as carboxylase Y.

After review and analysis of the included publications show that phosphoantigens do have the capability to cause proliferation of GDTCs. More research replicating results also providing evidence of these compounds working in vitro and additional reviews into the effectiveness to provide further evidence of GDTC proliferation

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An Investigation into the Chemical Properties Predictive of Blood-Brain Barrier Penetration

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Despite significant advances in neuroscience and an increasing global burden of central nervous system (CNS) related conditions[1], the number of drugs approved for marketing in this sector is dwindling.[2] One challenge in the development of CNS drugs is crossing the blood-brain barrier (BBB). This, amongst other reasons, means that translation of drugs from pre-clinical studies to humans often fails.[3]

The aim of this paper is to explore the chemical properties of successful CNS penetrant drugs to identify trends and compare them to the extent of brain penetration. This will allow identification of the chemical properties which most reliably predict good CNS penetration and help guide future drug discovery to reduce failure rate.

A rapid literature review was conducted using multiple databases. Chemical properties and brain penetration measurements were extracted from papers then analysed and compared.

Results: Lipophilicity displays the strongest correlation with brain permeability. Aqueous solubility and polar surface area (PSA) have relatively strong correlations with brain permeability. Brain permeability increases as lipophilicity increases and as aqueous solubility and polar surface area decrease. Molecular weight (MW) has very little correlation with brain permeability.

The mode number of hydrogen donors was 2 (35.5%). 98.5% of compounds had 4 or less hydrogen donors. Average number of hydrogen donors was 1.97. The most common numbers of hydrogen acceptors were 2 (24.2%) and 7 (22.6%) and 96.8% of the compounds had 7 or less hydrogen acceptors. 4.37 was the average number of hydrogen acceptors.

CNS drug developers should focus on increasing lipophilicity and decreasing aqueous solubility and polar surface area to efficiently increase brain permeability. This will reduce failure rate and the translation of drugs from pre-clinical trials to use in humans.

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Rapid review: Do dietary polyphenols from tea benefit cardiovascular health in humans?

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Tea is widely consumed around the world and is one of the most popular beverages after water, and the wide range of claimed health benefits[1-4] are a reason for research into this area, with results which could benefit the many. With lots of contradicting evidence from studies and varying quality of literature, this paper aims to review the current knowledge on the benefits of tea polyphenols specifically on cardiovascular health such as stroke and CHD.

A total of 1341 records from 2010 onwards were obtained from Ovid Medline, PubMed and Scopus and were screened and quality checked using CASP checklists and exclusion criteria. Following this process, eleven papers were subjected to critical analysis.

RCTs were of low quality (n=3) and the majority of cohort studies were focused on Asian populations, thus reducing the applicability to worldwide populations. Papers revealed varying results, with both green and black tea showing statistically significant inverse associations with CVD such as stroke (HR 0.80 (0.73, 0.87)), heart disease and other CV diseases. However, contradicting results from studies were also reported. Tea may reduce the risk of developing different types of CVD depending on gender and geographical location. Preference of green tea over black to improve CVD risk remains inconclusive.

Better quality RCTs with larger sample sizes are required in populations around the world to explore impacts of ethnically and socially diverse populations in order to confirm a strong association between tea consumption and CVD risk around the globe. Future research should also aim to investigate the tea polyphenol content, and other dietary sources of polyphenols in individuals when investigating CVD mortality and morbidity. Better research methodologies need to be articulated in order to obtain high quality and reproducible results. More research should be conducted in western populations as well as in black and ethnic minorities.

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A rapid review to explore the stability and formulation of Atracurium for NHS bulk manufacture and aseptic preparation into ready-to-use syringes.

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Atracurium is a neuro-muscular blocking agent with highly selective and competitive properties, most commonly used in intensive care units for sedation, intubation and ventilation. It also has uses as an adjunct in general anaesthesia.[1] Atracurium is favoured due to its non-dependence on kidney elimination[1]. During the COVID-19 pandemic, there has been a vast increase in the use of Atracurium, which has led to a supply disruption alert being issued.[2] Atracurium is currently only available in 2.5ml and 5ml ampoules and 25ml injection vials.[3] A rapid review was conducted to identify whether Atracurium could be mass produced and whether it could be prepared into pre-filled syringes for easier access and to avoid ward level manipulation.

Searches were conducted in SCOPUS, EMBASE, PUBMED and MEDLINE databases. Due to the niche subject, there was no date or language limit applied. Exclusion criteria included papers not focused on the use of Atracurium for intubation or sedation purposes relevant to COVID-19. Conference papers and studies conducted in community settings were also excluded. Quality and risk of bias was assessed using CASP checklists and the Joanna Briggs Institute Critical Appraisal Checklists.

A total of 3932 papers were identified and a total of 15 were used in the final report. It was not possible to perform a meta-analysis due to the differences in the studies. Overall, it was identified that Atracurium can be pre-filled into syringes in its undiluted from and will remain stable for longer than current manufacturer recommendations.

There was not a lot of data found on bulk manufacture to definitively determine whether it is possible. However, with further research and laboratory-based experiments, bulk manufacture could be experimented and the principles relating to stability that have already been identified could be applied to determine stability, safety and expiry.

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Assessing the efficacy of convection enhanced delivery (CED) compared to systemic drug delivery in the treatment of brain cancers: a rapid review of pre-clinical studies

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Glioblastoma multiforme (GBM) is a form of aggressive primary malignant brain cancer that originates from glial cells of the brain, with a 5-year survival of 5%. The current therapy includes surgical resection (where

possible), radiotherapy and concomitant temozolomide (TMZ).[1] Studies have shown that GBM is showing resistance against TMZ[2], indicating a clear need for novel treatments.

Convection enhanced delivery (CED) is an innovative technique, allowing delivery of therapeutics directly to the tumour through a catheter. CED allows drug delivery past the blood-brain barrier (BBB), therefore opening the doors to repurposing other chemotherapeutics that do not permeate the BBB and enables an increased drug concentration to reach the brain tumour resulting in improved therapeutic efficacy.[3] There is currently no systematic overview of all the pre-clinical data assessing the degree of therapeutic benefit from CED in comparison to systemic administration.

PubMed, SCOPUS and Web of Science were searched using specific search terms, then selection criteria were used to obtain pre-clinical articles of relevance, with a negative control and a direct comparison of CED vs systemic administration. A PRISMA flow diagram was utilised, resulting in 489 articles being narrowed down to 8.

Six out of 8 articles illustrated that CED was more therapeutically beneficial than systemic administration. Liposome encapsulated drugs resulted in a higher median survival time compared to non-liposome encapsulated drugs indicating the advantageous effect of liposomes, where PEGylated liposome doxorubicin had the highest median survival.[4] No toxicity was associated with any of the drugs used, except for carboplatin at a high dose.

Although chemotherapeutics and formulations i.e., liposomal need to be refined during future work, this research showed the benefit of CED compared to systemic administration for the treatment of GBM. Pre-clinical data implicates better assimilation of GBM which can be carried forward into clinical trials.

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An explorative study into the adherence to Prescribing Safety Indicators (PSIs) by general practices in Wales at health board and cluster Level.

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In the UK, several sets of Prescribing Safety Indicators (PSIs) have been developed. These indicators aim to identify patients at significant risk of prescribing error. In 2018, the All Wales Medicines Strategy Group (AWMSG) implemented a set of PSIs as part of a new strategy to support safe and optimised prescribing in Wales.[1] A subset of PSIs are assessed in this study; areas of focus include contraindications in beta-blocker prescribing and women's health. The aim was to assess the adherence to these PSIs by general practices within Wales by investigating the patterns and prevalence of high risk prescribing.

Anonymised, quantitative prescribing data was collected prospectively by AWMSG using the NHS Wales Informatics Service audit tool. The data was presented as patient numbers at cluster level and analysed retrospectively. Disease prevalence, population demographics, prescribing of medicines and their presence on health board formularies were explored as potentially confounding factors.

Analysis at Wales, health board and cluster level identified a number of spatial and temporal trends for each indicator. The principal findings include two statistically significant outliers. Firstly, the number of patients prescribed combined hormonal contraceptives with a history of thrombosis in Penderi was found to significantly decline over the data collection period, representing improved adherence. Secondly, the number of female patients prescribed sodium valproate were found to be consistently high in Afan.

Areas like Afan that require further improvement could benefit from augmentation of this broad data collection with a focussed audit at surgery level. Future work could support Welsh audit reports and primary care programmes by incorporating data on hospital admissions and accessing patient level data through the audit

tool.[2,3] By generating hypotheses, future research can build upon the ideas discussed. It is hoped this research may allow AWMSG to ask smarter questions relating to the research they are conducting.

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Investigating the barriers to deprescribing antipsychotics in dementia patients: a rapid review and content analysis

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Dementia, characterised by cognitive impairment, is a progressive, irreversible syndrome.[1] Behavioural and psychological symptoms of dementia, besides cognitive impairment, adversely affect prognosis and include psychosis, affective symptoms, hyperactivity, and apathy.[2] Despite adverse effects, antipsychotics are frequently inappropriately maintained to manage these symptoms. The term deprescribing signifies actively discontinuing medicines whose harms outweigh benefits,[3] such as antipsychotics in dementia. There are barriers, however, to successful deprescribing in practice. This review aims to compile and appraise qualitative literature reporting the antipsychotic deprescribing barriers in dementia.

Four databases were screened to retrieve relevant literature: Embase, Medline, Scopus, and Web of Science. Papers were distilled to the most relevant ones by duplicate removal, screening against eligibility requirements and for significance to the aim. Appraisal was integrated to assess the validity, degree of bias, and clinical applicability of these studies. Study characteristics and barriers were extracted, with barriers constrained into themes by content analysis. This review followed simplified systematic review methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol.[4]

Fifteen reports covering 2014 to 2020 were reviewed, comprised of seven methodological designs distributed across eight demographic regions. Publications examined antipsychotic use in dementia or cognitively impaired patients in long-term care facilities and the community. Thirty-nine barriers emerged from three themes: awareness, beliefs and attitudes, feasibility. Barriers identified by health professionals, relatives, and patients included inter-physician communication breakdown, low dementia literacy, and inadequate non-pharmacological interventions.

This review highlights that the first step to reduce inappropriate antipsychotic use in dementia is overcoming the deprescribing barriers. Consistent with the literature, barriers were interconnected. Barriers remained unchanged across the dates and demographic regions covered. High-quality non-pharmacological interventions, reduced healthcare restraints, and improved dementia education are future suggestions to overcome the barriers identified. Barriers reported by psychiatrists, neurologists, junior doctors, and pharmacists need investigating through qualitative surveys.

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Safety and efficacy of 5mg/kg vs. 7mg/kg once daily gentamicin dosing in adults: A rapid systematic review

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Gentamicin, an aminoglycoside antibiotic primarily used to treat Gram-negative bacteria, is potentially toxic in high concentrations. It has become common practice to give gentamicin as a single daily dose to achieve a drug-free period between administrations and reduce accumulation. This method has been optimised by implementing nomograms that determine dosing intervals. The Urban-Craig nomogram[1] for 5mg/kg and the Hartford nomogram[2] for 7mg/kg are both utilised widely. A recent report suggested that a higher dose may be required to combat new wild-type organisms.[3] The Swansea Bay University Health Board guidelines[4] currently provide access to the Urban-Craig nomogram for 5mg/kg and the question arises as to whether this is the most appropriate dose.

A rapid systematic review was undertaken to provide evidence to investigate this inquiry. In particular to look at relative toxicity and relative efficacy of the two dose regimens. A search was conducted in four databases, finding 499 papers. These papers were screened and 17 studies were identified as relevant.

Sixteen studies were based in hospital ward settings and there was a mix of prospective and retrospective designs. Twelve papers investigated efficacy in some form, ten looked at nephrotoxicity and six had results on ototoxicity.

There is evidence to suggest that ototoxicity is caused by long therapy durations rather than high gentamicin concentrations. Nephrotoxicity appeared to be higher with 7mg/kg doses, which supports the use of a lower dose. There was no clear evidence to suggest a difference in efficacy between the two regimens. The exemption to this being conditions where distribution of gentamicin in the body is impacted or when bacteria demand a higher inhibitory concentration. It is concluded that the 5mg/kg dose should remain as the recommended regimen but access to 7mg/kg nomograms should be provided for complex conditions.

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The impact of OTC antibiotics on antibacterial resistance

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

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

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

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

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A Survey into the Opinions of MPharm Students on the Multi-Sector Pre-Registration Year

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In the UK to become a registered pharmacist, it is required to complete a four-year master's degree (MPharm) at university followed by a 52-week paid placement in practice, known as pre-registration training.[1] The number of multi-sector pre-registration placements have increased annually in England and due to increase in Wales, with Wales adopting a fully multi-sector programme starting in 2022.[2,3] The aim of this study was to obtain the current views of MPharm undergraduates prior to commencing their pre-registration programme.

The opinions' of MPharm students across each of the four years of study at four purposively selected schools of pharmacy were obtained via an online survey distributed by a gatekeeper from each school. A favourable opinion was by Cardiff School of Pharmacy & Pharmaceutical Sciences Ethics Committee.

A response rate of 19% (n=336/1776) was achieved. There was a majority in favour of multi-sector pre-registration placements, compared with single sector, with 54% (n=181) saying they would prefer to see three sectors (hospital, community, and general practice) in a multi-sector pre-registration, even though there were concerns with the current three-sector model with 4 months in each sector. This study also found a lack of awareness of current multi-sector placements.

This study has shown that current students indicated a range of views on the content and duration of a multi-sector pre-registration. A limitation of this study is that only four schools of pharmacy were contacted, which leaves the opportunity for a UK wide study, over several years to build a picture on how the opinions of MPharm students change as the pre-registration training changes[4], and the effect this has on the future framework of the training of pharmacists in the UK.

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A Computer-Based Visualization and Diversity Analysis of The Antiviral 'Chemical Space'

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Antivirals represent profitable and successful pharmaceuticals, with >90 approved pharmaceuticals[1], blockbuster-achieving revenue, and reductions in global mortality rates for HIV and Hepatitis C infections. However, side-effect profiles[2], the emergence of novel pandemics and drug-resistant viral strains demand rapid testing of existing and novel effective treatments, to avoid increases in mortality. Therefore, clear models are needed that visualises the space where each antiviral occupy. This study aims to visualise the chemical space[3] and diversity of antivirals according to physicochemical (PCP) and topological parameters.

21279 ChEMBL molecules across 10 antiviral and 1 FDA datasets were extracted and pharmaceutically relevant physicochemical and topological properties e.g., molecular fingerprints and scaffolds were calculated. Compounds were included if they inhibited viral targets and had more than one FDA approved inhibitors.

Boxplots and Principal Component Analysis were used to determine and summarize physicochemical property distributions. Common scaffolds were plotted with a bar chart and visualised using ChemDraw. The molecular similarity between encoded fingerprints was calculated and plotted using cumulative distribution function curves.

Overall, results showed similar PCP distributions between neuraminidase and DNA polymerase inhibitors and between HIV and HCV targets. NS5B inhibitors showed greater chemical overlap with anti-HIV drugs which were hydrophobic and molecularly flexible. Measures of drug hydrophilicity were found to be primarily responsible for physicochemical diversity in the chemical space and all PCPs showed moderate inter-variable correlations. Anti-influenza drugs displayed lowest antiviral molecular similarity whilst HIV and HCV drugs were virtually identical, however further study is needed to elucidate whether bioactivities are similar. Scaffold diversity was lowest among NS3-4A and neuraminidase inhibitors, indicating instead higher diversity in side-chain modifications.

Further studies are needed to elucidate whether structurally similar compounds yield similar bioactivities. Novel scaffolds were identified which in conjunction with physicochemical data, could yield druggable lead compounds among protease and DNA Polymerase datasets.

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A rapid review on the use of cytotoxic drugs delivered by ambulatory care

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Cancer is a highly prevalent disease in the UK. Chemotherapy treats 28% of newly diagnosed patients, using cytotoxic agents.[1] Chemotherapy administration tends to require hospital attendance; however, ambulatory care allows treatment on an outpatient basis.[2] This is currently desirable with the emergence of the coronavirus disease 2019 limiting hospital capacity and requiring hospital visits to be minimised.[3,4] This rapid review investigates whether the use of cytotoxic drugs can be increased in ambulatory care. The drugs investigated were assigned by the University Hospital of Wales (UHW), Cardiff. Namely, vincristine/etoposide/doxorubicin combined as part of the EPOCH regimen; ifosfamide with mesna; doxorubicin; cisplatin and daunorubicin.

MEDLINE, EMBASE and Web of Science databases were searched for literature and results were exported to EndNote X9. Literature was reviewed against an inclusion and exclusion criteria. To document the process of excluding papers the PRISMA (Preferred Reporting of Systematic reviews and Meta-Analysis) flow diagram was used.

8 papers were included in the review, all of which used Computerised Ambulatory Delivery Devices (CADD) to deliver at least one of the drugs relevant to the review. The review focusses on CADD pumps as these are the devices used by UHW.

The use of vincristine/etoposide/doxorubicin combined as part of the EPOCH regimen, ifosfamide with mesna and cisplatin were well documented and results suggested they could be successfully implemented in ambulatory care. There was a lack of literature which included the use of doxorubicin monotherapy, and any real evidence of daunorubicin being administered to patients and so there was insufficient evidence to indicate these agents should be implemented in an ambulatory care setting. To improve the likelihood of successful implementation, sufficient resources should be provided to the patient to ensure the patient is educated on the use of the device. These findings will be reported to UHW.

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Endosomal escape strategies in vaccine development: Where do we stand? A rapid review

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COVID-19 was announced as a pandemic in March 2020 and with over 2 million deaths, scientists are working hard to develop effective vaccine to protect individuals from this virus.[1] Apart from COVID-19, other serious diseases such as cancers, HIV and influenza are reasons why scientists have put effort into vaccine development. Modern strategies involve vaccines carrying cargoes (DNA or RNA) encapsulated in suitable vectors, and upon entry into the target cells, promote escape from endosome to manufacture proteins, producing an immune response.[2] The COVID period has highlighted vectors such as viruses and nanoparticles but less is known regarding the use of these in the clinical trials space. The aim of this work was to review the different strategies employed for endosomal escape of the vaccine cargo with a view to better understanding how this filed of research has developed in the last decade.

The records were obtained from Clinical Trials.gov and PubMed and were screened and selected via EndNote-X9, eligibility criteria, CASP checklists and PRISMA flow diagram. Thirteen clinical trials are included in this rapid review with six from COVID-19 vaccines and seven from vaccines targeting other diseases.

Most of the vaccines utilise membrane fusion as the endosomal escape mechanism. These vaccines deliver cargoes such as engineered DNA and modified mRNA through the help of appropriate vectors like lipid nanoparticles, viral vectors and bacteria-derived vector.

In this rapid review, most vaccines targeting other diseases halted at early study phases although they were started years ago while COVID-19 vaccines proceed to later study phases and three from the COVID-19 vaccines have been approved to be tested on local populations of various countries in less than a year. This rapid review proves that vaccines involving endosomal escape strategies are making progress and have the potential to thrive in the market.

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2. Varkouhi AK, Scholte M, Storm G, Haisma HJ. Endosomal escape pathways for delivery of biologicals. Journal of controlled release. 2011;151(3):220-8.

Can haemodialysis frequency be safely reduced during a pandemic in risk-stratified patients without a significant effect on blood pressure and fluid retention?

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The COVID-19 outbreak necessitated a change in the way many NHS services were run, in order to protect staff and patients. The South West Wales (SWW) Renal Unit was no exception. This service cares for patients with chronic kidney disease, who are also likely to suffer with other diseases, making them especially vulnerable to the symptoms of COVID-19.[1,2] Patients usually attend the dialysis unit three times a week, however in order to reduce their exposure to COVID-19, certain patients were reduced down to twice weekly dialysis for 9 weeks.

Patients were stratified according to their risk of complications into three cohorts. Patients were weighed before and after each dialysis session and their blood pressure taken and recorded. The difference in body weight was calculated between dialysis sessions (assuming 1kg of body weight = 1L of fluid).[3] This data was compared to data collected before and after the 9-week period to determine if the reduction in haemodialysis frequency had an effect.

During the 9-week intervention period, the amount of fluid accumulated by the patients increased significantly, however there was no effect on systolic blood pressure. Whilst the increase in fluid was statistically significant, clinically, it affected just 3% of the patients, causing them to be hospitalised. This low proportion could be due to the fact that these patients are particularly well controlled and motivated to take part in their own care.

The intervention proved to have a positive effect on COVID-19 cases, with no evidence of transmission in the Carmarthen dialysis unit, and 6 cases recorded in total. This study has shown that dialysis frequency can be safely reduced for 9 weeks, provided that the patients are risk-stratified appropriately. These outcomes can be used in the event of a future pandemic to advise on suitable stratification.

1. Levy J, Brown E, Lawrence A. Oxford Handbook of Dialysis. Fourth ed. Oxford: Oxford University Press; 2016.
2. Welsh Government. All Wales COVID-19 workforce risk assessment tool. 2020 [accessed 9 Dec 2020]. Available from: https://gov.wales/sites/default/files/publications/2020-12/covid-19-workforce-risk-assessment-tool-08-12-2020_0.pdf
3. Renal Dietician Team. Managing your fluid balance. 2020 [accessed 22 Dec 2020]. Available from: https://www.ouh.nhs.uk/patient-guide/leaflets/files/68498Pfluid.pdf

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Inhibition of vitamin D 24-hydroxylase (CYP24A1) as a potential therapeutic strategy: A systematic review

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Many medical conditions, such as cancers and autoimmune diseases, have been associated with overexpression of vitamin D 24-hydroxylase (CYP24A1), an enzyme that breaks down calcitriol, the active form of vitamin D. [1, 2] This results in a depletion of calcitriol, which has been identified to exhibit activity such as antitumour effects.[3] This rapid systematic review aims to evaluate whether inhibition of CYP24A1 has potential as a therapeutic strategy.

Three databases, Pubmed, Web of Science and Scopus, were scoped to identify literature evidence from 2010-2020 of CYP24A1 inhibition with respect to medical conditions. Publications were scanned and then fully screened for eligibility based on inclusion and exclusion criteria. Data from the remaining relevant studies was extracted and summarised.

15 publications were included in this systematic review, in which a variety of CYP24A1 inhibitors and therapeutic areas have been researched. The selectivity/specificity, molecular modelling and biological effects of the CYP24A1 inhibitors has been analysed to assess their therapeutic potential.

CYP24A1 inhibition enhances calcitriol's antitumour activity in numerous cancers and demonstrates potential as prospective interventions for chronic kidney disease and secondary hyperparathyroidism. [(3, 4)] However, there are hurdles which need to be overcome, including designing selective inhibitors to reduce the risk of side effects such as hypercalcemia, prior to studies and use in humans. Nevertheless, inhibition of CYP24A1 as a therapeutic intervention has attractive potential and this should drive future research.

1. St-Arnaud R. CYP24A1: Structure, Function, and Physiological Role. In: Feldman D, Pike JW, Adams JS, editors. Vitamin D. 3rd ed. London: Elsevier; 2011. p. 43-56.
2. Schuster, I. et al. Selective Inhibitors of Vitamin D Metabolism - New Concepts and Perspectives. Anticancer Research. Anticancer Res. 2006;26(4A):2653–2668.
3. Zhalehjoo N, Shakiba Y, Panjehpour M. Gene Expression Profiles of CYP24A1 and CYP27B1 in Malignant and Normal Breast Tissues. Mol Med Rep. 2017;15(1):467-473. doi: 10.3892/mmr.2016.5992
4. Nagamani S, Muthusamy K. A Theoretical Insight to Understand the Molecular Mechanism of Dual Target Ligand CTA-018 in the Chronic Kidney Disease Pathogenesis. PLoS One. 2018;13(10):1-26. doi: 10.1371/journal.pone.0203194

Challenges for the WHO's strategy for a 'leprosy-free world': A rapid review on the issues and opportunities surrounding the treatment of leprosy

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Leprosy, or Hansen's Disease, is caused by *Mycobacterium leprae* or *Mycobacterium lepromatosis*.[1] Leprosy mainly affects the peripheral nerves, the skin, the eyes and mucosa of the upper respiratory system.[1] The WHO announced that leprosy had been 'eliminated' (incidence of less than 1 in 10,000) in 2000.[1] Despite this,

it is still present and prevalent in many countries in the world. This review aims to discern the treatment issues which are preventing or hindering the full eradication of leprosy and supply possible solutions.

Databases were searched for papers which were relevant to the review's aims. These papers were then put through the PRISMA method to determine their true usefulness and relevance. Of the original 112, a final 15 papers were retrieved and studied in depth.

The final 15 papers supplied information the following topics: drug resistance, Dapsone Hypersensitivity Syndrome (DHS), Pure Neurotic Leprosy (PNL), Unified Multi-Drug Therapy (uMDT), alternative treatments and variations and inconsistencies of practise.

The major points drawn from this information base that drug resistance is climbing, cases of DHS and PNL are significant in prevalence that heath care professionals must be educated to be vigilant for them, uMDT is still yet to be used despite its theoretical benefits, alternative treatments are available but are yet to be fully implemented and that variations between guidelines and actual practise are occurring even within a single city. Patient compliance along with HCP and patient education is key for the resolution of these issues.

1. WHO. Leprosy. 2019. [accessed 8 Oct 2020] Available from: https://www.who.int/en/news-room/fact-sheets/detail/leprosy

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Evaluating health inequalities in primary care prescribing of antidepressants in Wales in 2015 and 2019

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Health inequalities are changes in healthcare practices between populations due to factors such as age and socioeconomic status.[1] A commonly recognised health inequality is "postcode prescribing". In Wales, 12% of the Welsh population reported having a "mental health condition", depression being the most reported.[2] National guidance was published to standardise the treatment of depression in the United Kingdom. It suggests what agents are to be used and lists agents such as dosulepin that are not recommended.[3] The aim of this study is to indicate if national guidance is implemented at the 64 primary care clusters in Wales.

Data was acquired from the comparative analysis system for prescribing audit database. This provided the annual prescribing figures of antidepressants at the 64 clusters in Wales for 2015 and 2019. Data was extracted for drugs in specific antidepressant classes, as detailed in current national guidance[3], and exclusions were made for specific formulation strengths that are not indicated for the treatment of depression.

The antidepressant class prescribed in the greatest quantity was the selective serotonin reuptake inhibitors. Results suggest that prescribing in the majority of clusters adhered closely to NICE guidelines. In 2019 the Dwyfor cluster prescribed the highest quantity (25 items per 1000) of dosulepin (a drug that NICE advise should not be prescribed) in Wales. At the national level the prescribing of new generation antidepressants e.g. vortioxetine, was notably higher in England (2.2 items per 1000 people) compared to Wales (0.6 items per 1000).

Some potential health inequalities between clusters could be rationalised. However, two identified health inequalities are candidates for further investigation. Greater prescribing of dosulepin in Dwyfor is an important inequality as the drug is associated with cardiotoxicity. Additionally, the higher use of vortioxetine in England compared to Wales is a national inequality and suggests reduced access to the new-generation antidepressants in Wales. Future studies should investigate the health inequalities discovered in this study.

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2. Statistics for Wales. Welsh health survey 2015: health status, illnesses, and other conditions. Cardiff: Welsh Government; 2016.
3. National Institute For Health And Care Excellence. Depression in adults: recognition and management. CG90. London: National Institute For Health And Care Excellence; 2009 [accessed 14 Oct 2020]. Available from: https://www.nice.org.uk/guidance/cg90

The association of complement factor H deficiency with abnormal coagulation parameters- a rapid review

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Complement factor H (CFH) is a regulator of the alternative pathway of complement where it protects the host from complement-mediated damage. CFH deficiency is rare, however a deficiency of the protein can result in excessive complement activation and disease. Studies have described several interactions between CFH and coagulation factors suggesting a potential role for the CFH within the coagulation system.[1,2] The aim of this review was to review the literature presenting CFH deficient patients and to identify whether coagulation dysfunction is evident amongst the patients to contribute to the understanding of CFH's potential role in coagulation.

The PubMed and Scopus databases were searched to identify papers describing CFH deficient patients. Papers were included where a case report was presented in relation to a patient with a clear CFH deficiency.

Ultimately 24 papers were eligible for inclusion including 32 patients. All 32 patients were diagnosed with pathologies which included 21 cases of atypical haemolytic uraemic syndrome (aHUS). The most frequently described coagulation abnormality was thrombocytopaenia, identified in 17 of the 32 patients all of which were diagnosed with aHUS. Three case reports described the results of coagulation tests, with only one doing so during a CFH deficient state prior to treatment. Both the thrombin clotting time and fibrin degradation products were slightly elevated in this patient (FDP).[3]

Ultimately, the identified coagulation abnormalities included thrombocytopaenia, renal thrombotic microangiopathies and slightly elevated FDP and thrombin time in one patient. However, they were all identified in CFH deficient patients with aHUS and it remains unclear whether the abnormalities are a consequence of the disease mechanism or a direct result of the CFH deficiency. This review summarises the literature regarding CFH deficient patients and has highlighted a lack of coagulation investigation in CFH deficient patients particularly those with pathologies other than aHUS.

1. Dzik S. Complement and Coagulation: Cross Talk Through Time. Transfusion medicine reviews. 2019;33(4):199-206. doi: 10.1016/j.tmrv.2019.08.004
2. McCluskey G, Davies G, Velounias R, Hughes TR, Morgan BP, Preston R, et al. Complement Regulator Factor H is a cofactor for thrombin in both pro-thrombin and anticoagulant roles [abstract]. Res Pract Thromb Haemost. 2020;4
3. Thompson RA, Winterborn MH. Hypocomplementaemia due to a genetic deficiency of β1H globulin. Clinical and Experimental Immunology. 1981;46(1):110-9.

An investigation into the effect of RyR2 mutations on channel Ca^{2+} sensing in arrhythmia: a rapid review

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Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), with an estimated prevalence of ~1:10000,[1] results in cardiac arrest during exercise or acute emotion in the absence of structural cardiac abnormalities.[2] Beta-blockers are recommended; however, symptoms are often inadequately controlled with ~30% of patients requiring additional therapies. Even with beta-blocker therapy, there is a 19% mortality rate,[3] therefore, more effective treatments are required. Mutations in RyR2 are a major contributor to the disease[4] and so this rapid review aims to evaluate and critically appraise research concerning RyR2 dysfunction in CPVT.

PubMed, Embase, and Medline were consulted to examine the literature and relevant data were extracted into EndNote. The studies were assessed for eligibility and a PRISMA flow diagram was constructed. The articles were further screened and subjected to quality assessment. The relevant information was then included in this review.

This study included 13 papers. This rapid review summarises any possible influence of mutation location on RyR2 dysfunction, mutation influence on changes in cytosolic or luminal Ca^{2+} sensitivity, the potential role of phosphorylation in unmasking mutant dysfunction, and whether the mutations affect accessory protein binding and expression.

There is no clear link between the location of the mutation and the effect of the mutation. Mutation generally leads to an increase in Ca^{2+} sensitivity. This can be on the luminal or cytosolic side of the channel, or both. PKA phosphorylation is required to unmask the dysfunction of certain RyR2 mutant channels but not in others. There may be altered accessory protein binding, which can influence RyR2 function, but not all studies investigated this phenomenon. In conclusion, CPVT-linked mutant RyR2 channels are mainly gain-of-function, but show considerable variability, making it difficult to develop new therapies that target the channel directly, indicating a need for a personalised medicine approach.

1. Imberti JF, Underwood K, Mazzanti A, Priori SG. Clinical Challenges in Catecholaminergic Polymorphic Ventricular Tachycardia. Heart Lung Circ. 2016;25(8):777-83. doi: https://doi.org/10.1016/j.hlc.2016.01.012
2. van der Werf C, Wilde AAM. Catecholaminergic polymorphic ventricular tachycardia: from bench to bedside. Heart. 2013;99(7):497. doi: 10.1136/heartjnl-2012-302033
3. Liu N, Ruan Y, Priori SG. Catecholaminergic Polymorphic Ventricular Tachycardia. Prog. Cardiovasc. Dis. 2008;51(1):23-30. doi: https://doi.org/10.1016/j.pcad.2007.10.005
4. Wehrens XHT. The molecular basis of catecholaminergic polymorphic ventricular tachycardia: what are the different hypotheses regarding mechanisms? Heart rhythm. 2007;4(6):794-7. doi:10.1016/j.hrthm.2006.12.016

Prevalence of Antipsychotic use within care homes and their effect on polypharmacy

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Inappropriate antipsychotics (APs) usage in dementia is targeted for deprescription in the light of widespread use within care homes combined with preceding studies demonstrating APs radically increase risk of cerebrovascular adverse events.[1] AP use has been previously observed in 1/5 of care home patients[2], a frail, high-risk group owing to their predisposition to co-morbidities, and subsequently greater requirement for pharmacological treatment. Hence it is necessary to investigate whether AP use aggravates this already intensified level of polypharmacy. This study analyses the prevalence of antipsychotics use within care homes and how they exacerbate polypharmacy.

A quantitative analysis was carried out on drug administration data of 329 care home patients within 12 homes across Wales, England, and Scotland. Total AP users were recorded alongside their prescribed duration. Prescribing trends were explored utilising a weeks' worth of administration data, comparing polypharmacy levels in AP and non-AP users, and percentage patients receiving painkillers, antidiabetics, and drugs within several neuroactive classes. Anticholinergic effect on cognition (AEC) scores were calculated to illustrate the consequence of the intensified polypharmacy stimulated in AP use.

25.5% of patients received an antipsychotic during the 9-month data extraction, 61% of which for over a 56-day duration. AP users averagely received more drugs compared to non-users (6.53 vs 5.21), simultaneously receiving nearly double the number of neuroactive drugs (1.22 vs 0.69). Anxiolytics and sedatives were dramatically more prevalent amongst AP users, taken by 36.1% compared to only 12.0% of non-users. 59.0% of AP users scored AEC scores of 2-4, compared to 8.3% of non-users.

AP users demonstrate exacerbated polypharmacy and higher likelihood to be co-administered neuroactive drugs, worsening anticholinergic burden, reinforcing the need for antipsychotic deprescribing. Further studies are necessary to explain the impetus behind these prescribing trends, and survey prescribers to explore whether this level of polypharmacy is clinically justified.

1. Ralph SJ, Espinet AJ. Increased All-Cause Mortality by Antipsychotic Drugs: Updated Review and Meta-Analysis in Dementia and General Mental Health Care. J Alzheimers Dis Rep. 2018;2(1):1-26. doi: 10.3233/ADR-170042
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3. Shah SM, Carey IM, Harris T, Dewilde S, Cook DG. Antipsychotic prescribing to older people living in care homes and the community in England and Wales. Int J Geriatr Psychiatry. 2011;26(4):423-34. doi: 10.1002/gps.2557

A rapid review of the barriers to deprescribing antipsychotics and the solutions to them

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Approximately one-third of people with dementia are prescribed antipsychotics for management of BPSD despite limited evidence of their efficacy long-term.[1] Therefore, antipsychotics need to be deprescribed to reduce polypharmacy and improve quality of life. This rapid review was conducted with the aim of identifying existing solutions to deprescribing antipsychotics and determine what barriers exist to their implementation.

MEDLINE, EMBASE, Web of Science and Scopus were searched for relevant literature. The titles and abstracts were then screened against the inclusion and exclusion criteria. Data on design, country, barrier identified, solution and outcomes were extracted from each study. Risk of bias and quality of evidence was assessed using CASP checklists.

Of the 3544 papers identified, 18 papers were included in this review. A meta-analysis could not be performed due to heterogeneity between the studies. The interventions investigated were medication review (n=3), education (n=3), other (n=3), medication review with education (n=3), medication review and specialist involvement (n=1), education with other (n=1) and multicomponent intervention (n=1). The remaining 3 studies were systematic reviews which investigated multiple interventions.

Medication review with education was found to be the most effective intervention to reduce antipsychotic use. However, more research needs to be done into the barriers to implementing the intervention in order to successfully deprescribe antipsychotics in people with dementia.

1. Kirkham, J. et al. 2017. Antipsychotic Use in Dementia: Is There a Problem and Are There Solutions? *Canadian Journal of Psychiatry* 62(3), pp. 170-181. doi: 10.1177/0706743716673321

Remote Consultations: An investigation into the views and experiences of healthcare professionals.

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Owing to the COVID-19 pandemic, the need for healthcare professionals to consult with patients remotely has never been greater.[1] With many face-to-face consultations unable to occur, virtual and remote consultations provide an alternative for healthcare professionals.[2] However, there is limited evidence indicating how to support healthcare professionals in adapting to these changes in healthcare settings. This project aims to investigate the experiences of healthcare professionals and how they can be better supported to consult remotely.

Due to the nature of research, qualitative methods were deemed most appropriate, in the form of semi-structured interviews. Participants were all healthcare professionals, identified by their involvement in the independent prescribing course at Cardiff University. A purposive approach was used to select participants with the aim to select from a range of health professions and a gatekeeper method was used before direct contact was made. Interviews were carried out online and subsequently transcribed and thematically analysed.[3] As a result, key themes emerged and were explored.

Six interviews were carried out; 4 with pharmacists and 2 with nurses, all undertaking a postgraduate prescribing qualification. Results showed participants had a number of concerns including challenges with building rapport, obtaining a clinically complete and accurate picture on which to base decisions, and technology issues. However, participants suggested remote consultations are more advantageous for the patient as this eliminates the need for them to leave their home, and advantageous to healthcare professionals in terms of recording and audit purposes.

The study concluded that healthcare professionals have a number of barriers to overcome to ensure the standard of remote consultations are that of face-to-face consultations, but highlighted many benefits for both patient and healthcare professionals. Healthcare professionals would likely benefit from education surrounding building rapport and assessing patients without a visual and more effective technology and resources would be valuable.

1. NICE. 2020. Clinical guide for the management of remote consultations and remote working in secondary care during the coronavirus pandemic. Available at: https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/specialty-Guide-Virtual-Working-and-Coronavirus.pdf (Accessed 11 January 2021)
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3. Braun, V. and Clarke, V. 2006. Using thematic analysis in psychology. Qualitative Research in Psychology 3(2), pp. 77-101. doi: 10.1191/1478088706qp063oa.

Welsh Language and Initial Education and Training of Pharmacists: perceptions of Pre-registration pharmacists with formal Welsh language undergraduate training

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After the revision of the Welsh Language Act in 2011, Welsh has the same legal status as English in Wales[1], thus ensuring that every public sector had to provide Welsh services.[2] Welsh language teachings has been deemed important by the Welsh language Commissioner to the healthcare profession.[3] Since 2015 the Welsh School of Pharmacy have included structured Welsh language teachings within the course[4], but the pre-registration year does not currently have any official Welsh language training.[3] The aim of this project is to explore the perceptions of pre-registration pharmacists on the provision of Welsh language during the initial education of pharmacists.

Qualitative one to one interviews were used as the data collection tool. Purposive, non-probability sampling was utilised to identify participants meeting the inclusion criteria, which included; 1) Welsh Speaking Pre-registration Pharmacists, 2) undertaking their Pre-registration training in Wales, 3) undertaken formal Welsh language training during the Mpharm. The interviews were conducted online via Zoom and transcribed verbatim. The data was analysed thematically.

Four main themes were identified during the study. 1) Communication identifies confidence and the societal pressure and judgement surrounding the Welsh language. 2) Patient centred care shows how important it is to ensure patient centred care. 3) Undergraduate (Mpharm) course that identifies developments for the Mpharm course and lastly, 4) Pre-registration year shows how the training received by pharmacists can incorporate more Welsh language or bilingual teaching.

This study has identified the need for enhanced Welsh language teaching and training to support the provision of Welsh language services and patient centred care. The communication aspects of the course are most appropriate, for example OSCEs and clinical skills. Further work needs to be done in the future after the improvement and inclusion of Welsh language training to see if there has been an impact in patients' lives.

1. Llywodraeth Cymru: Welsh Government. Welsh Language (Wales) Measure 2011. 2016 [accessed 3/11/2020]. Available from: https://law.gov.wales/culture/welsh-language/welsh-language-wales-measure-2011/?lang=en#/culture/welsh-language/welsh-language-wales-measure-2011/?tab=overview&lang=en
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3. Llywodraeth Cymru: Welsh Government. More than just Words… Action plan 2019-2020. Jul 2019 [accessed 31/10/2020]. Available from: https://gov.wales/sites/default/files/publications/2019-07/more-than-just-words-action-plan-2019-2020.pdf
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A rapid review of pre-clinical literature investigating the efficacy of polymers as local drug delivery systems for the treatment of glioblastoma multiforme

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Glioblastoma multiforme (GBM) is a rapidly developing stage IV brain cancer[1] with an incidence rate of 3.19 per 100,000 people and is the most common malignant primary brain tumour diagnosed.[2] Survival prognosis of this cancer is extremely poor, with just a 5% survival probability after five years.[3] There is therefore a clear need for the identification of new, effective means of treatment in order to improve this prognosis.

While much research has focused on the clinical utilisation of one such polymer device (Gliadel),[4] there is currently no systematic overview of the wide range of pre-clinical studies that have been performed with polymeric implants. Publications were taken from the search databases Scopus, Web of Science and PubMed with only studies in pre-clinical stages matching pre-determined inclusion/ exclusion criteria being included.

The aims were to critically appraise existing literature in a systematic format to prove/disprove the hypothesis that local polymeric drug delivery provides real benefit against GBM.

All six publications included showed statistically significant improvements in median survival of rats treated with intracranial local delivery of polymers compared to no treatment when initiated on day 0 of tumour implantation. Half of applicable papers showed improvement in the local delivery groups when treatment was initiated on day 5. Results from papers comparing local vs systemic delivery varied, but still showed promise for the local delivery of polymers.

The outcomes of this review support the hypothesis that local drug delivery via polymers reduces glioma growth and/or increases animal survival compared to no treatment and/or systemic delivery of treatment to a degree. There are still issues with the use of polymers such as the need to optimise polymer material and drug diffusion properties, but further research into the area should be conducted as it shows a lot of promise.

1. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathologica. 2016;131(6):803-20. doi: 10.1007/s00401-016-1545-1
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3. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiology Biomarkers and Prevention. 2014;23(10):1985-96. doi: 10.1158/1055-9965.EPI-14-0275
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A retrospective analysis of the calls made from social care to the NHS 111 Clinical Support Hub

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Receiving urgent care through an out of hours service like NHS 111 is an example of unscheduled care. Use of unscheduled care is increasing, is expensive and is one of the most pressured part of NHS.[1] Failures to plan care in an appropriate and timely manner as well as difficulties experienced by carers because of complex care needs, high turnover rates of staff in social care and limited investment in developing their skills[2] may contribute to calls to 111. This study aims to analyse the volume and types of calls NHS 111 receives from social care to identify the most common reasons for calling and whether these relate to medication and treatment.

A retrospective analysis of routinely collected NHS 111 call logs from the Aneurin Bevan University Health Board was undertaken. All calls made to the 111 Clinical Support Hub (i.e., needing clinical input) between October 2019 and September 2020 by a carer or for those living in a care home were included. Quantitative analysis was used to generate descriptive statistics and qualitative inductive thematic analysis was used to explore the consultation.

A total of 2583 calls were received during the study period. Symptoms presentation was the most common reason for calling but there were many other reasons including requiring death verification, terminal care, needing catheter and dressing care as well as medication queries and medication requests. A range of call outcomes were also seen, with self-care being the most advised.

The study provided insight into the calls the clinical support hub receives from social care. Findings suggest that some of the calls could have been potentially avoidable and recommendations were suggested as to how changes could be made to existing systems, policies and guidelines to reduce the number of avoidable calls.

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A rapid review of the evidence base for the value of proactive testing in reducing COVID-19 transmission

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COVID-19 (Coronavirus Disease 2019) is one of the biggest public health problems facing the world today. With COVID-19 having unusual clinical features in comparison to other related viruses (e.g. a large asymptomatic proportion of cases, 43% of COVID-19 cases)[1], there is a need to define what institutions can do to prevent localised outbreaks. This rapid review aims to find the value of proactive testing within closed cohort populations, and if proactive testing would be worth implementing in congregate settings.

Three databases were used: Web of Science, SCOPUS, and Google scholar to find literature evidence of proactive testing within closed cohort populations. Studies were screened for their eligibility based on inclusion and exclusion criteria. Augmentation of database searches using 6 live data dashboards from universities and grey literature (e.g Color)[2], as the situation is rapidly developing.

A total of 11 studies were included in the review, based on their eligibility criteria. This review considers: the transmission dynamics of COVID-19 within a population; the impact of varying testing frequency, sensitivity, and turnaround time; the combination of other interventions required to control an outbreak and the feasibility of testing regimens.

Proactive testing can detect cases (57% before symptomatic onset)[3] earlier, and when they are the most infectious, compared to symptomatic screening. However, the impact of testing is brought into question when other interventions used within institutions are considered., especially within a university environment, non-case based interventions can prove more useful (e.g. universal mask wearing)[4]. Varying testing frequency and the turnaround time have similar impacts on how efficacious proactive testing is, whereas test sensitivity is not as important, within a population. Further studies need to investigate the impact of proactive testing on data which can be applied readily to the community, but this is difficult within a time limited pandemic situation.

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Understanding the Cardiff MPharm student experience of online examinations during the COVID-19 pandemic

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The emergence of COVID-19 on 31st December 2019[1], lead to universal university campus closures in the UK and a transition to remote education and examinations.[2] At Cardiff School of Pharmacy and Pharmaceutical Sciences, the 'Spring' examinations 2020 were changed from traditional invigilated closed-book examinations to online non-invigilated open-book examinations. The aim of this study is to explore Cardiff MPharm students' experiences and opinions of online non-invigilated open-book 'Spring' examinations in 2020.

Seven focus group discussions were conducted; 5 with MPharm4 students and 2 with MPharm3. A total of 25 participants were recruited. Focus groups were conducted on Zoom, audio and video recorded, and transcribed verbatim. Data was thematically analysed to identify the following themes and sub-themes (i) The impact of change - student attitudes and feelings before the 'Spring' exams, exam preparation, equality and fairness; (ii) School support for transition to virtual environments - support for learning, guidance for virtual exam preparation, managing expectations and communication (iii) Virtual exam structure - exam split section layout, virtual exam format, and technical submission requirements (iv) Remote physical environment - distractions, informality and flexibility, and technology issue (v) Future exam preferences.

This study highlights the diversity of individual MPharm student experiences during the COVID-19 pandemic. Further research is required to determine if these experiences are generalised. Moreover, this study identifies the need to review MPharm examinations and formulate an online examination format that compliments the diverse student preferences reported in these results and the emerging published literature.

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Resulting Properties of Droplet Interface Bilayer (DIB) Model Membranes.

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Droplet interface bilayers are artificial model membranes that form between lipid-monolayer encased water droplets in an oil phase.(1) They are useful for the study of membranes and testing pharmaceuticals.[1] Various studies in the literature suggest that resulting DIB membrane properties vary depending on its composition.[2,3] This work describes the research aimed at conducting a rapid literature review for finding any relationship between the composition and the resulting physical properties of DIBs in terms of contact angle (Θ) and surface tensions (γ_m, γ_b).

The search terms “droplet interface bilayer AND contact angle OR surface tension” were used for scoping publications from different databases. Articles were reviewed against set eligibility criteria and an adapted PRISMA flow diagram for exclusion was followed. Reports brought forward went through exhaustive analysis and the data extracted was compared based on the lipophilicity of the lipids and oils, for which CLogP (a measure of lipophilicity) was used.

A total of 12 studies were included in this review. Data on the lipids, oil and aqueous phases, droplet size, and method of formation was extracted. As well as Θ, γ_m and/or γ_b data. The results suggested that the method and the lipid and oil composition chosen for DIB formation have an influence on the Θ, γ_m, and γ_b, which support suggestions made in other studies.(2,3) Concerning lipid variations, the higher the lipophilicity of the lipids used to create the DIB platform was, the higher were the values obtained for Θ, γ_m, and γ_b. However, no trend was found for oil phase variations.

In conclusion, this project supports that DIB composition influences its properties. However, the different studies did not use the same characteristics (e.g. different droplet sizes used), which represents a limitation. Therefore, further systematic experimental studies are needed to confirm findings and deeply investigate this area.

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What changes are needed to Cardiff MPharm placements for the new 5 year-year integrated programme with incorporated independent prescribing training?

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The General Pharmaceutical Council have initiated new learning standards for a 5-year integrated pharmacy undergraduate programme which includes independent prescribing training.[1] Thus, an important aspect to consider is how MPharm students would have sufficient practice exposure for the skill acquisition to be competent pharmacist independent prescribers (PIPs) as there is currently limited placements in MPharm programmes.[2] There is limited research investigating MPharm placements. Therefore, this study aims to explore the views of students and PIPs on MPharm placements to identify areas of improvements as well as recommendations towards this change.

As views and experiences were important for this study, qualitative research methods were adopted and semi-structured interviews were chosen for its flexible structure. Following ethical approval, participants were recruited by purposive sampling with inclusion criteria: Cardiff University MPharm year 3 and 4 students, and alumni PIPs. Interviews were conducted and video recorded with consent then transcribed verbatim. Resulting transcripts were analysed by thematic analysis.

Participants expressed views on placements such as community pharmacy being valued less favourably than other types of placements. Improvement suggestions included a need for longer placements for ensuring sufficient time to settle into the workplace environment and build work relationships. For the change: shadowing of prescribers, increased inter-professional learning, patient assessment skills, and more use of educational practices including case-based discussions were recommended.

Students views of placements closely resembled previous research[3,4], and as this study indicated, highlighted the benefits of increased preparation of placement supervisors for effective placement provision and quality assurance of site.[3,4] Furthermore, identified a need for using learning standards to assign placement tasks[4]. Repeating this study after standards are fully implemented and changes to placement structure have been made would be useful to explore perceived benefits. To conclude, gaps in placements were identified and potential changes that would contribute to better-prepared students to be PIPs.

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Histone Deacetylases, Their Inhibitors and Alzheimer's Disease: A Rapid Review

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As the aging population grows ever larger, diseases such as Alzheimer's Disease are becoming more prevalent with the amount of people living with Alzheimer's set to more than double over the next twenty years in the UK alone.[1] It currently has no cure and this review aims to explore a possible solution through inhibition of histone deacetylases (HDACs). These enzymes are linked to memory and cognition in the brain and therefore implicated in Alzheimer's disease.[2] The first inhibitors developed bound to all types of HDAC unselectively (pan-inhibitors) leading to unpleasant side effects that limit their use.[3] This review explores selective inhibitors that bind to the types of histone deacetylases that are most implicated in Alzheimer's disease pathology.

Three scientific databases were searched; SCOPUS, EMBASE and MEDLINE, to collect *in vitro* and *in vivo* findings for selective inhibitors on Alzheimer's disease pathology, as well as to ascertain the inhibitors' chemical structures. Studies were chosen through screening based on inclusion criteria/exclusion criteria, and once included were subjected to critical analysis as well as extraction of relevant data for comparisons.

Nineteen studies were identified in accordance with inclusion/exclusion criteria, for which the *in vivo/vitro* properties, chemical structures, toxicities and IC_{50} values for relevant HDACs of their most promising inhibitor candidate(s) were reported, to compare with pan-inhibitors.

Six inhibitors were identified with statistically significant positive effects on cognitive performance in rodent Alzheimer's disease models, as well as encouraging effects on Alzheimer's disease pathology. More inhibitors were developed selective to HDAC 6 than Class I HDACs. Selective inhibitors were associated with lower toxicity than the pan-inhibitors, with HDAC 6 selective examples being the least toxic. The review suggests that with more in vivo testing and drug optimisation, selective HDAC inhibitors could be a viable treatment for Alzheimer's disease.

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

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

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

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

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

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Understanding the Behaviour Deficits Induced by Pre-formed Fibrils in the Rodent models of Parkinson's Disease - A Rapid Review

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Rodent models of Parkinson's disease (PD) are essential in the pre-clinical testing of new therapeutics. Previous models fail to fully encompass, face, predictive and construct validity.[1] The recently emerging a-synuclein preformed fibril (PFF) model shows an improvement in construct validity, yet the appropriateness of the behavioural tests used in this model have not been considered. This review aims to assess how the methodology of PFF administration, and the behavioural test used, impacts the degree of behavioural deficit observed.

A literature search was performed across the databases: Medline and EMBASE, the records were then extracted into EndNote-X9. The studies were reviewed against an eligibility criterion, a modified PRISMA

diagram was followed to manage the exclusion of studies. The ARRIVE 2.0 'Essential 10'[2] guidelines were then used as an assessment of quality for the included studies.

Of the 559 studies extracted, 18 performed intracranial administration of PFF into the nigrostriatal pathway and fulfilled the inclusion criteria. There was a clear preference for the use of a mouse host, 9 behaviour tests were carried out in mouse studies and 6 in the rat. The most frequently conducted motor task was the rotarod, but the wire hang and the pole test, showed the most consistent and clear deficits. Importantly the quality check highlighted a clear lack of transparent reporting across the field.

An appropriate behaviour test needs to be a compromise between a measurement of the models face validity[3] and observing a clear deficit. The pole test encompassed both a measure of bradykinesia[4], a cardinal symptom of PD, and produced the clearest deficits, making it the most appropriate test to be used. Overall, this is still an immature field, especially in rat hosts, and this review has highlighted the importance of accurate reporting in surgical procedures, and behavioural tests to fully validate the model.

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An Evaluation of the Switch from Heparin to Taurolock Hep500 as a Lock Solution in Tunnelled Haemodialysis Central Venous Catheters in the South West Wales Renal Unit

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Catheter related infections and occlusions are the most common complications associated with mortality and morbidity in haemodialysis patients therefore minimising the clinical effects of these complications is important.[1-2] Guidelines recommend locking central venous catheters with a solution with combined antimicrobial and anticoagulant properties however, to date, no gold standard catheter line-lock has been identified. This study aims to evaluate if the switch from Heparin to Taurolock Hep500 as a catheter line-lock in the South West Wales renal unit resulted in fewer catheter related infections and occlusions and was financially beneficial.

Data was extracted from the central renal database for all central venous catheters constructed for haemodialysis between 1/08/2018 and 31/07/2020. Lines were grouped by initial line lock resulting in a Taurolock Hep500 group with 66 lines and a heparin group with 145 lines. Both groups were compared for infective and thrombotic complications and cost.

Catheter infection rates were higher in the heparin group than the Taurolock Hep500 group with 0.63 and 0.42 infections/1000 catheter days respectively. Catheter occlusions were significantly higher in the Taurolock Hep500 group with a greater proportion of lines requiring rescue therapy (15/66 cf. 18/145) corresponding to 1.66 and 0.80 lines needing Alteplase/1000 catheter days in the Taurolock Hep500 and Heparin groups respectively. (Odds ratio 0.42, 95% CI 0.22, 0.80) Financially, the switch appeared beneficial with cost of catheter complications being 2x higher in the Heparin group.

Infection results suggest that Taurolock Hep500 was clinically beneficial, supporting trends shown by other studies, due to its antimicrobial component.[3] Line occlusion results however suggest that the switch resulted in an increased requirement for rescue therapy in Taurolock Hep500 lines. Further investigation is required to determine why Taurolock Hep500 resulted in more catheter occlusions as results are counter to evidence from the Taurolock Hep500 manufacturer and surrounding literature.[4]

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Welsh Language Education and Training of Pharmacists: An Investigation into the Perceptions of Pre-registration Pharmacists with Formal Welsh Language Undergraduate Training.

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With over a quarter of the Welsh population being Welsh speakers[1], and Welsh and English sharing the equal legal status in Wales[2], patients have the right to access healthcare through the medium of Welsh. Whilst there are methods in place to facilitate this, there is much room for improvement. This investigation explores how the provision of Welsh language education during the MPharm course and pre-registration year benefits pharmacy students and pre-registration pharmacists, and how it can be improved to facilitate better care to Welsh speaking patients.

The study was done using a qualitative research method, with exploratory, non-probability, purposive sampling. Semi-structured interviews were conducted with each participant individually over Zoom and were recorded and transcribed verbatim. The data was analysed using thematic analysis to provide sub-themes and main themes. The main themes were: Welsh provision in MPharm, Welsh provision in pre-registration, and patient experience.

Several suggestions were made on ways Welsh language education could be improved – by providing introductory lectures for Welsh speaking students, providing translation resources, and by increasing opportunities to practice with other Welsh speakers. It also discussed ways that Cardiff University could expand its role to increase the number of pharmacists able to provide care in Welsh.

While current Welsh language education on the MPharm course appears to be of good quality, more is required for students to feel as comfortable with the course content in Welsh as they are in English. Pre-registration training must improve to include the Welsh language as pre-registration pharmacists would feel far more confident providing services in Welsh if they were to receive additional support. Further research is needed to pinpoint exact and efficient ways to improve Welsh language education during MPharm and pre-registration training.

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The use of tuberculosis rapid diagnostics in people living with human immunodeficiency virus in sub-Saharan Africa: a rapid review

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a leading cause of death worldwide, with people living with HIV (PLHIV) at an increased risk of active disease and mortality.[1] The current gold-standard for diagnosis is culture with results taking several weeks.[1] Rapid diagnostics return results within hours yet many rely on sputum samples, limiting their use in sputum-scarce PLHIV.[2] Over half of high TB burden countries are in sub-Saharan Africa[1]; the need for electricity limits rapid diagnostic use where healthcare resources are limited. This review aims to appraise tuberculosis rapid diagnostics for their point-of-care use in this population alongside cost considerations.

Six databases, Google Scholar and Cardiff University Library were searched for relevant literature. Included studies were conducted in sub-Saharan Africa on adult and adolescent participants with HIV. Sensitivity and

specificity data were required for inclusion. Studies were screened and assessed for quality before data was extracted for analysis. The PRISMA flow diagram assisted this process.[3]

Eighteen included studies assessed five rapid diagnostics. Sensitivity and specificity data were reported with comparisons made by CD4 cell count (representing severity of HIV disease). Gene Xpert, a sputum-based nucleic acid amplification assay[1], showed the greatest sensitivity and specificity across all stages of HIV. Cost comparisons for Gene Xpert and TB-LAM (a urine-based assay detecting lipoarabinomannan antigen[2]) showed the latter less costly.

All rapid diagnostics assessed in this review have limitations restricting their point-of-care use. Gene Xpert should be used when available, with urine TB-LAM replacing the less effective tuberculin skin test in this population[4] as a screening tool. Combining HIV and TB services will increase diagnostic yield, making progress towards the eradication of TB. Further studies confirming these findings in other low-resource settings will enhance recommendations for use. Novel diagnostics are needed with a focus on simultaneous antibiotic resistance testing and battery-operated equipment.

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A Conventional Content Analysis of NSS Free-text Comments Relating to the MPharm Degree at Cardiff University in the Period from 2016/17 to 2019/20

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Free-text comments submitted in response to the National Student Survey are viewed as an aid to universities in making changes designed to improve current and prospective students' learning experiences via the feedback obtained regarding students' positive and negative experiences.[1] Acting on student feedback may improve subsequent cohorts' satisfaction.[2] This study aims to use free-text comments in response to NSS surveys of Cardiff MPharm students in the period 2016/17 to 2019/20 to identify their views on their experiences during the degree.

Using conventional content analysis, free-text comments from 203 final-year students were initially coded at a high level as either positive or negative, according to the nature of the opinions conveyed within each comment. Inductive codes were then generated to indicate the specific areas or issues of the course to which the comments referenced. The codes which shared similarities were combined to form categories. The number of comments assigned to each category were tabulated to compare the frequency of individual categories across the four years.

This study indicates that a growing number of students perceive greater placement opportunities within the course to be a vital improvement required to further enhance the learning experience. Whilst results also highlighted the importance to students of having access to helpful, enthusiastic, and friendly staff. The number of students providing negative comments relating to assessments fell over the period.

This study provides a detailed understanding of students experiences of the Cardiff MPharm. Therefore, this study has been useful in identifying several elements of the degree that a number of students have reported as being beneficial during their studies, together with some suggestions for review and/or change.

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A Rapid Review: What are the factors affecting the patient journey and patient care when receiving an unlicensed medicine in the UK?

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Background, aim/objectives: The patient experience from diagnosis to treatment is referred to as 'the patient journey'[1], a concept formulated to improve patient care. Licensing of medicines for treatment by the MHRA is based on the demonstration of quality, safety, and efficacy.[2] However unlicensed medicines (ULM), also referred to as "specials", are often used in healthcare. This study aims to develop an effective search strategy to collect relevant published work to understand the factors that may influence patient care/journey when receiving ULMs in the UK. To identify patient-, disease-, and healthcare-specific factors including pharmaceutical issues that help or hamper the provision of good healthcare using ULMs.

Methods: A rapid review method search of seven major scientific databases was performed using established search terms. Imported all search results to Mendeley software to create a master database. Selection and screening were based on designed inclusion and exclusion criteria. Results were presented using PRISMA diagrams and the Mixed Methods Appraisal Tool was used for appraisal.

Results: Of the 2172 studies found in chosen databases, 22 studies remained after selection processes (8 qualitative; 12 quantitative, and 2 mixed methods). The main outcomes identified were the lack of awareness of what unlicensed medicines are and a lack of understanding of the associated risks and benefits by patients and the general public, or even healthcare professionals. There were also cost issues, increased incidences of ADRs, and safe supply problems in primary and secondary care.

Discussion/ conclusion: All factors identified within 22 studies were based on the views or experiences of patients, the general public, or healthcare professionals. The doctors, pharmacists, and prescribers have a responsibility to be aware the initiated medicines were unlicensed and potential implications associated with ULMs use, as well as educate and provide adequate information to patients.[3]

1. Beleffi E, Mosconi P, Sheridan S. The Patient Journey. In: Donaldson L, Ricciardi W, Sheridan S, Tartaglia R, editors. Textbook of Patient Safety and Clinical Risk Management. Cham: Springer International Publishing; 2021. p. 117–27. [accessed 14 Oct 2020]. Available from: 10.1007/978-3-030-59403-9_10
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3. Donovan G, Parkin L, Brierley-Jones L, Wilkes S. Unlicensed medicines use: a UK guideline analysis using AGREE II†. Int J Pharm Pract. 2018 Nov 27;26(6):515–25. doi: 10.1111/ijpp.12436

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

Exploring Gamma-Delta T Cells Activation Strategies

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Exploring the staff perceptions on the impact of Electronic Prescribing Medicines Administration in the South West Wales Renal Unit

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Effect of bacterial adhesion on biofilm formation for medical devices

Rory Flynn and P Prokopovich
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Discovery of COMT-Resistant Parkinson's Disease Treatments

John Foster and Y Mehellou
Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, King Edward VII Avenue, Cardiff CF10 3NB, Wales, UK

Antimicrobial surfaces in hospital settings and role of adhesion

Lucia Fraschetti and P Propokovich
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An Evaluation of the Community Pharmacy Emergency Medicines Supply Service in Wales from May 2016 to August 2020

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Microbial infection, role of bacterial adhesion for dental application

Jamie Szeto and P Prokopovich
Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, King Edward VII Avenue, Cardiff CF10 3NB, Wales U.K.

What are the views of Independent Prescribing Pharmacists and commissioners on the community pharmacy pilot Independent Prescribing Service?

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Microbial colonisation of orthopaedic resulting in infection

Rory Williams and Dr Polina Prokopovich
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An evaluation of enhanced community pharmacy services across Wales in the past year

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Is combination therapy more effective than using a single chemotherapeutic drug for local treatment of glioblastoma?

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Glioblastoma (GBM) is an aggressive, heterogeneous and infiltrative cancer that is commonly associated with a poor prognosis. Moreover, recurrence is regularly observed, despite using the gold-standard treatment for GBM. Impermeability, in relation to the blood-brain barrier, and systemic toxicity of the drugs are both dose-limiting factors that prevent effective treatment of this tumor. Recent development of local drug delivery systems has tried to overcome these issues. This systematic rapid review aims to determine whether using combination therapy locally (on pre-clinical animal glioma models) is a better method of treatment than monotherapy.

Three online databases were searched systematically, identifying publications that tested locally given combination therapy against monotherapy in animal glioma models. Papers were screened using pre-set inclusion & exclusion criteria. The studies were quality-assessed using a 12-point scale, with median survival, long-term survival and key findings of each being extracted. For papers in which data were presented only graphically, values were estimated by measurement from the publication.

Five publications were identified that met the inclusion & exclusion criteria. Combination therapy significantly prolonged survival in four out of five papers when compared to untreated control and monotherapy test groups. Local drug delivery systems proved to give sustained release of the drug over a suitable time period, and caused no adverse reaction in the animals. The type of glioma model used seemed to affect how the drugs affected the survival rate of the animals. Diffusion rate for each drug in the brain parenchyma was also found to be different. The quality of papers used had no correlation with the significant increase of overall survival.

The majority of the papers used in this review proved that locally delivered combination therapy is more effective for treating glioblastoma than monotherapy. Although, more pre-clinical research needs to be conducted regarding this topic to form a concrete perspective.

The anti-proliferative and anti-metastatic effect of statins on breast cancer: a rapid systematic review

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Breast cancer is the most common type of cancer among women and is associated with high morbidity and mortality rate worldwide. Breast cancer treatment represents an active area of research due to its limited treatment options, specifically on the aggressive phenotypes of breast cancer. In the past decades, lipophilic statins have gained attention due to their potential anti-cancer effects on solid tumours. This study aims to systematically review and evaluate the anti-proliferative and anti-metastatic effect of statins on breast cancer in the current literature. Four databases were searched to assess the anti-proliferative and anti- metastatic activity of statins on breast cancers. After screening the titles and abstracts of 1160 studies, 27 were included in this study. Of these, thirteen studies focused on proliferation, six studies on metastasis and eight studies focused on both. This study was constructed following PRISMA guidelines and critically evaluated following CASP guidelines. The results of these pre-clinical studies indicated that lipophilic statins inhibited breast cancer proliferation through inducing cell cycle arrest and inhibiting proliferation-related signalling pathways. In addition, lipophilic statins inhibited key steps in the metastatic cascade such as invasion, EMT, dormancy, secondary growth leading to the inhibition of metastasis. Furthermore, these agents also reduced the level of the stem cell population within the cell line population. These pre-clinical studies support a potential anti-cancer effect of statin specifically on aggressive breast cancer cells and metastasis. Further validation through clinical studies would position these agents as valuable anti-cancer therapeutics given their well-tolerated and wide spread use.

The role of miRNAs in development of cisplatin resistance in ovarian cancer; A rapid systematic literature review

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Ovarian cancer (OC) is the most common gynecological malignancy in the western society, as estimated to affect 1.2% of women. It shows a considerably low 5-year survival rates upon diagnosis and initial treatment, as OC is often not diagnosed until the disease is advanced. The management of OC involves cytoreductive surgery followed by chemotherapy. Cisplatin is considered as the first line treatment for OC showing success in improving prognosis. However, most patients relapse and develop resistance to cisplatin after prolonged treatment regimen. Resistance mechanisms are mostly associated with genetic and epigenetic aberrations. miRNA dysregulation plays a pivotal role in modulating the response of OC to cisplatin.

This rapid review was initiated in a 12-week period undergoing a thorough literature search. The online databases PubMed and Web of Science were used to search for the relevant articles investigating the role of miRNAs in mediating resistance of OC to cisplatin drugs.

The results of the literature search revealed the potent impact of miRNA in mediating response of OC to cisplatin. Different species of miRNAs were investigated and exhibited various effects on OC response to chemotherapy. However, the effect of miRNAs is dependent on their targets, which in turn determine whether the miRNA would exhibit a tumour promoting or suppressing effect, as the function of miRNAs is to bind and silence gene transcripts. Moreover, most of the miRNAs investigated were found downregulated and thus maintaining high levels of their downstream targets. miRNA-mediated oncogenic pathways activation contributes to poor prognosis and development of chemotherapeutic resistance in OC. Therefore, the regulatory mechanisms involving miRNAs in OC require thorough investigations to reveal the sub-molecular factors controlling the development and progression of the disease.

Is doxorubicin cardiotoxicity mediated via effects on the cardiac sarcoplasmic reticulum Ca^{2+} load?; A rapid literature review

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Doxorubicin (DOX) is one of the most efficient chemotherapeutic agents, and is approved for various cancer treatments, including solid and haematological malignancies. Despite its highly beneficial effects against cancer, doxorubicin treatment can lead to cardiomyopathy and congestive heart failure, thus decreasing its clinical utility. This rapid literature review aims to identify the underlying mechanisms of action of this drug on cardiomyocyte sarcoplasmic reticulum (SR) Ca^{2+} load, through its effects on three integral proteins which set this: the cardiac ryanodine receptor (RyR2), the Ca^{2+} storage protein calsequestrin (CSQ2) and the SR Ca^{2+} pump (SERCA2a).

Three electronic databases were searched (PubMed, Medline and Embase) in order to find papers evaluating the mechanisms of integral SR proteins and regulation of Ca^{2+} load after doxorubicin treatment. The search strategy used in the review produced a total of 585 papers. From these, 19 papers met the inclusion criteria and were selected for critical appraisal and analysis.

Search findings highlighted several mechanisms of DOX action on the SR. DOX causes a significant increase in Ca^{2+} leak via RyR2 followed by sustained inhibition at high concentrations. This occurs due to either the direct binding of DOX to the RyR2 channel or activation of reactive oxygen species (ROS), which triggers an increase in RyR2 phosphorylation at the calmodulin kinase II (CaMKII) site. DOX treatment disrupts the RyR2-CSQ2 interaction, leading to increased luminal Ca^{2+} sensitivity of the channel, and hence SR Ca^{2+} leak, leading to low SR Ca^{2+} levels. In some studies DOX also lowered expression levels of SERCA2a, resulting in low levels of Ca^{2+} in the SR, and high cytosolic Ca^{2+} levels. To conclude, dysregulation of Ca^{2+} homeostasis contributes in the induction of DOX cardiotoxicity and heart failure.

Issues in the management of cancer related pain in care home residents: a rapid review

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Cancer is a degenerative disease which has higher incidence rates in older adults. Since there is an aging population in many developed countries rates of cancer are likely to increase. Care homes are a long-term, reliable, alternative to informal home care, where staff may be better equipped to deal with age related diseases like cancer. A common symptom that requires management in cancer patients is cancer related pain – but the regulation and management of cancer associated pain in the care homes setting has not been explored extensively. This review therefore will explore pain management of care home residents with cancer.

A rapid review of three databases: MEDLINE, EMBASE, and Scopus, was carried out to identify papers including search terms that would retrieve papers discussing the topics of cancer medicine, pain management and care homes. The papers retrieved were limited to 2014 to present (2020) because of a systematic review written by Drageset et al (2014) which was the most recent review paper to discuss published research on this topic, the review would also be used to establish the baseline for developments in this field of research after the publishing of the Drageset paper. Then a Critical Appraisal Skills Programme (CASP) Checklist was performed to assess the bias of selected papers.

A PRISMA flowchart was used to detail included papers and excluded papers, the reasons behind exclusion and the numbers excluded by criteria. Out of 66 possible papers, 15 were taken for review. These 15 papers included eight cross-sectional studies, 4 cohort studies, 2 systematic reviews (one being the Drageset et al. paper), and 2 longitudinal studies. For the included papers, 8 were from the United States, one in Sweden, two in Norway, one in Germany, one in Canada and one in Australia. No research was retrieved for the UK. Furthermore, not all papers were comparable, therefore, meta-analysis could not be performed.

The research reviewed by this paper has explored the issues surrounding pain management including dementia related pain tolerance, racial discrepancy in pain management, specifically in non-Hispanic black and Hispanic residents, and use of opioids in resident pain management. There is an improvement found in pain management with the use of PAINAD and PACSLAC methods to discern pain in residents with dementia, the discrepancy against racial demographics is likely due to racial poverty in nursing homes in America, and there is a need to tailor cancer pain to the degree of pain prevalence in patients, the use of PACSLAC in a more universal sense may allow better pain diagnosis in all residents, especially since it has a suggested therapy for residents. The lack of UK research also needs to be addressed.

ST6Gal-I induced a2,6-sialylation in colorectal cancer invasion and metastasis

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Sialic acids are a family of carbohydrates synthesized in the cytosol and then transferred to the cell surface. They are located at the ends of glycolipids and glycoproteins, and they play important role in different biological processes such as cell adhesion, immune recognition, tumour invasion and metastasis. Increased sialic acid expression (hypersialylation) has been involved in several types of cancer. The enzymes responsible for the sialylation and the increased expression in cancer, are sialyltransferases. Although, there are different types of sialyltransferases this review chose to focus on β-galactoside-α2,6-sialyltransferase (ST6Gal-I). ST6Gal-I is known to be upregulated in many types of cancer, including colorectal cancer (CRC). With the use of two databases a number of 34 articles were chosen and included in this review, with the aim to present the relevant information available regarding ST6Gal-I induced α2,6-sialylation in tumour progression. The main findings showed that 1) one of the mechanisms causing high ST6Gal-I expression in CRC might be the ras oncogene, and 2) high expression levels of ST6Gal-I α2,6-sialylation are involved in increased invasion and metastasis, because the α2,6-sialylation of β1 integrins confers enhanced attachment to collagen-I giving the cells an invasive phenotype. Additionally, it was also presented that α2,6-sialylation of Fas receptor is involved in inhibition of Fas-mediated apoptosis. Another important discovery showed that the ST6Gal-I α2,6-hypersialylation of EGFR causes resistance to therapy of gefitinib. As well as radiotherapy resistance could possibly be caused due to Hypersialylation. The findings that ST6Gal-I overexpression and subsequently α2,6-sialylation are implicated in tumour metastasis, makes the ST6Gal-I a potential promising therapeutic target.

Is doxorubicin cardiotoxicity mediated in part via effects on the cardiac ryanodine receptor? A rapid systematic literature review

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The anthracycline drugs such as doxorubicin are widely used in the clinical treatment for various malignant cancers, such as breast cancer and leukaemia. However, cardiotoxicity is a severe and sometimes fatal adverse reaction of doxorubicin treatment, which limits the application of these drugs in tumour therapy. Although numerous experimental studies suggest that the mechanism of doxorubicin-induced heart damage is oxidation-dependent, many antioxidants do not appear to have a significant cardioprotective effect. Traditional cardiovascular treatments, such as beta-blockers and hypotensive drugs, also provide limited protection, and there is currently a lack of monitoring for the prevention and treatment of doxorubicin-induced heart damage. Accordingly, new therapeutic approaches are required to promote the sensitivity of cancer cells to DOX urgently. Previous research shows that DOX binds to the cardiac ryanodine receptor, altering its activity in a deleterious way. This systematic review aims to determine the mechanism of doxorubicin mediated cardiac ryanodine receptor dysfunction.

Three databases were consulted; Medline, Scopus and Embase, in order to find literature evidence. Studies were selected for their eligibility based on inclusion and exclusion criteria. After reading and inclusion of relevant studies , they were subjected to quality assessment, before data from all the included studies was extracted and variables assessed.

Data indicated several mechanisms for doxorubicin induced cardiotoxicity via effects on the cardiac ryanodine receptor, including changing expression and affecting regulatory protein interactions. These mechanisms need further investigation such that progress towards amelioration of these cardiotoxic effects can be made.

Are Members of the SLC39A family of Zinc Transporters suitable Therapeutic Targets for Breast Cancer?

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Zinc is the second most important essential heavy metal of great public health significance after iron. It is utilized in numerous biological processes in mammals and it is considered as a multi-purpose trace element, due to its participation in the activation of more than 300 enzymes. It also is involved with over 3000 transcriptional factors and 10% of the human genome is known to bind zinc. Recently, studies have highlighted the role of zinc and zinc transporters that is gaining momentum as a potential therapeutic target for cancer.

This rapid systematic review was conducted utilizing 5 databases (PubMed, Web of Science, Embase, Medline and Scopus), in order to evaluate whether there was an association between SLC39A zinc transporter (ZIP) family members and cancer progression and their role as potential drug targets for cancer. Searches were assessed using PRISMA flow diagram and checklist also PICO tool to provide of high-quality assurance for the data arising from each article.

Results demonstrated that ZIP6 expression levels were found to link with grade, size, and stage of breast cancer, indicating that it is a strong driving force toward malignancy; ZIP7 plays an important role in the cell survival of breast cancer, especially in tamoxifen resistant breast cancer cells; ZIP9 is significantly expressed in human tissue and up-regulated in breast cancer tissue; and ZIP10 is implicated in breast cancer cell invasion and metastasis. These findings demonstrate that ZIP6, ZIP7, ZIP9 and ZIP10 all contribute to human breast cancer progression. Therefore, the role of these zinc transporters provides novel diagnostic and therapeutic targets for breast cancer treatment.

Are members of the SLC39A family of zinc transporters good targets for the prevention of cancer metastasis?

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Cancer metastasis accounts for 90% of cancer-related morbidity and mortality however, at present, there are no licenced anti-metastatic therapeutic agents. As such, cancer metastasis represents an important area of unmet clinical need. This rapid review analyses literature from 5 independent databases to evaluate the potential of SLC39A zinc transporter (ZIP) family members as potential drug targets for the prevention of metastasis in common cancers. Following screening of 350 potentially relevant articles, 18 were included in this review, representing in vitro, in vivo and clinical data analysis. Findings implicated ZIP4, ZIP6, ZIP9 and ZIP10 as drivers of cellular migration and invasion. These phenomena were largely underwritten by ZIP-mediated epithelial-to- mesenchymal transition (EMT), with the exception of ZIP9 which officiates androgen-responsive GPCR signalling. Clinical data analysis, derived from both featured literature and independent expression database-mining, confirmed significant upregulation of these ZIP transporters in common cancers, however association with specific metastatic clinicopathological parameters was generally unconvincing. As such, although of biological relevance to metastasis, more substantial data will be required to affirm clinical relevance of ZIP4, ZIP6, ZIP9 and ZIP10 as anti-metastatic therapeutic targets. This research will be reliant on molecular resolution of complex post- translational regulation, governing activation and intracellular ZIP localisation, to facilitate development of ZIP isoform-specific expression analysis tools.

Specificity and Common Properties in The Development of Small Molecule Anti-Metastatic Agents; A Rapid Review

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Metastasis is a critical problem. It is the main cause of cancer morbidity and mortality. It is notoriously difficult to treat and is the main reason for treatment failure. Currently there are no treatments available for the specific targeting of metastasis even with the recent development of targeted therapies. The need for the development of an anti-metastatic agent is essential. The aim of this rapid review is to determine if there is an emerging strategy to the development of small molecule anti-metastatic agents.

A thorough literature search was carried out utilising several online databases: Scopus, Web of Science, and PubMed. Papers found were assessed first through a title and abstract screening and then through a full text screening. Relevant papers were extracted. From these relevant papers' structures and targets of small molecules, in vitro data, in vivo data, and clinical relevance were assessed.

Findings showed that there were no common properties in the structures of the molecules. However, they were found and tested in similar ways. The majority of molecules were assessed for their anti-metastatic activity as they had previously been shown to have an anti-cancer effect. The other molecules were assessed because they were found through screening to inhibit particular pathways. Most of the in vitro assays assessed for the same things, migration and invasion, even if the assays used were not the same. The in vivo data also showed that the studies used very similar imaging techniques to assess metastasis.

Whilst it can be seen in this review that there may be the potential emergence of a strategy in the development of small molecule anti-metastatic agents more data needs to be looked at in order to confirm this. It is also shown that there is a point in the timeline where metastasis is started to be looked at as a therapeutic outcome.

Local drug delivery systems as viable treatments for glioblastoma multiforme; an analysis of preclinical date

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Glioblastoma multiforme is the most common and most deadly form of brain cancer. Even with a combination treatment of surgical resection, radiation and adjuvant chemotherapy prognosis remains poor. Patients on average survive one year, with <5% reaching 5 years survival. In the last couple of decades treatment for brain cancers had been focussed on novel local delivery of chemotherapeutics. To date the Glidal wafer is the sole local delivery implant approved by the FDA for GBM treatment. It is considered a controversial treatment with minimal prolonged survival over standard treatment with severe toxicities experienced by patients. Thus, local delivery systems have room for development and improvement.

A rapid review was conducted to evaluate preclinical data investigating the efficacy of local drug delivery systems implanted intracranially into rat glioma models. A systematic search of Pubmed, Web of Science, and Scopus was preformed using keywords such as; 'preclinical', 'in vivo', 'wafer', 'microsphere', and 'local delivery'. Studies were assessed for eligibility based on specific inclusion and exclusion criteria. Median survival, tumour volume and adverse events were analysed for systemic and local drug delivery systems. A total of thirteen publications were included in the review.

Every publication demonstrated that administering chemotherapeutics directly into the tumour cavity prolonged median survival compared to the systemically treated conditions in rat glioma models. In terms of temozolomide six publications reported median survivals ranging from 23-36.5 days for systemic delivery and 34-107 days for local delivery methods. The local drug delivery systems were well tolerated with minimal adverse events observed across all studies. With further development and the progression to clinical trials these novel delivery systems may finally improve prognosis of GBM.

Is ZIP7/SLC39A7 from the family of SLC39A of Zinc Transporters a good therapeutic target for treating cancer?

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Zinc is a metal ion that is essential for normal functioning and regulation of cellular processes, including development, differentiation, and regulated cell death. Zinc levels in the body are maintained by two families of Zinc transporters; SLC30A and SLC39A. ZIP7 is part of the SLC39A family and is found on flattened membrane sacs(endoplasmic reticulum) that are involved in folding and transport of proteins. ZIP7 controls the release of zinc into cells when activated by tyrosine kinase CK2 which initiates growth signalling pathways. Aberrations in zinc signalling is implicated in diseases such as metabolic disorders, cancer, and neurodegenerative disorders. ZIP7 is shown to overexpressed by cancers to help them grow and avoid cell death. Hyperactivation of ZIP7 is prevalent and linked to the resistance of Tamoxifen, which is an anti-hormone treatment for breast cancer. This review aims to analyse whether ZIP7 could be a viable target in future treatment of cancers where high levels are observed as this is linked to a poorer outcome. Also, to see if it has potential as a diagnostic tool for resistance in breast cancer. This is an unmet clinical need and so could have an impact on further research using ZIP7 as a novel therapeutic target.

Anti-cancer effect of statins on breast cancer

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Breast cancer is the second most common cancer and in the UK has the highest mortality rate in women. Statins are drugs that reduce the serum cholesterol levels. There are many pre-clinical trials to support statins as anti-cancer agents due to their anti-angiogenic effect and their ability to induce apoptosis. This paper is a rapid review on the anti-cancer effect of statins in breast cancer.

This rapid review will review papers after 2008, women in clinical trials who have been diagnosed with breast cancer. This rapid review will have summarised 6 papers to review the anti-cancer effect in statins.

This paper showed that there is an association between statin and their effect on Ki-67 and CRP expression levels, especially in aggressive tumours. The dose of statins could matter on the desired outcome, although this could differ between statin dependent on their potency (i.e. low doses ideal for second and third generation statins and high doses for first-generation statins).

More trials are needed to investigate this. Based on the statins used in the rapid-review, there is an association between atorvastatin and the anti-cancer effect induced on breast cancer cells. However, more studies need to be carried out in order to draw a clear conclusion.

SPAK and OSR1 kinase inhibitors as potential Cancer Treatments

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SPAK and OSR1 are two protein kinases that are members of the germinal center kinase VI subfamily of the mammalian Ste20 (Sterile20)-related protein kinase family and they are closely related with each other. WNKs are also a family of four serine/threonine kinases WNK1, WNK2, WNK3 and WNK4. SPAK and OSR1 kinases are downstream targets of WNKs and two out of four, specifically WNK1 and WNK3 are strongly related with the functions of SPAK and OSR1.

These three kinases in combination with each other or on their own are involved in the regulation of a variety of pathways and cotransporters that ultimately lead to cancer initiation, progression, and cell invasion. SPAK and OSR1 are also found to be involved in hypertension. Pathways that are regulated by these kinases include among others, the TRPC6-NFAT pathway and the MAPK pathway. As for the cotransporters the most prominent ones are NKCCs which are mostly linked to WNK1 and WNK3. NKCCs refer to sodium (Na+), potassium (K+) and chloride (Cl-) cotransporters.

The aim of this rapid review was to collect information on how these two kinases are involved in cancer, which pathways and cotransporters are regulating and how and if they can be potentially used for the development of therapies. Research was conducted using three databases (PubMed, Scopus and ScienceDirect) and the most relevant papers were selected. The overall outcomes of the studies included in this review suggested that inhibition of their functions can give positive outcomes and potentially used as targets for the development of novel therapies for cancers. In a specific case though, that is mention in the results section, their expression and more specifically the expression of SPAK is vital instead of its inhibition for positive outcomes.

A Rapid Review: Specificity and Common Properties of Antimetastatic Small Molecule Agents

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In cancer, which is a big health problem on its own, since metastatic cancers negatively affect the course of the patient's treatment, and has a poor prognosis, it significantly reduces the patient's survival. The use of small molecule agents, one of the targeted cancer therapy ways, is one of the most effective methods for preventing metastasis. This rapid review is to provide an overview of the specificity and common properties of small molecule agents having antimetastatic effects and showing no cytotoxic effects in effective doses.

For this study, three online databases, PubMed, Scopus and Web of Science, were searched for articles evaluating in vitro and in vivo studies conducted with small molecule agents that could show antimetastatic effects without any cytotoxicity. After screening, 94 articles were included in the rapid review, all of which were antimetastatic studies. Based on the inclusion criteria specified in these databases, a search was done as per PRISMA and articles that did not comply with these criteria were excluded.

As a result of the searching conducted, eight articles meeting all the criteria were obtained and the small molecule agents NMac1, EB-3D, EHop-016, XC-591, ZINC69391 and analogue 1A- 116, YH-306, VS-6062 and Tivantinib were evaluated in here in regard of specificity and common features. Several of these molecules, which were carried out in different types of cancer and have different intracellular targets, target the same protein.

These small molecule agents did not have or show significant common features; however, it was seemed that they have various specific properties in terms of both their intracellular target proteins and the signalling pathways they affect. Nevertheless, the small molecule agents had antimetastatic effect, and showed no cytotoxicity since they were chosen according to search criteria.

All the small molecule agents studied in this review have been shown to exhibit antimetastatic effects without any cytotoxicity. Therefore, each is a promising antimetastatic agent; however, further studies need to be conducted in different types of cancer.

JQ1: A rapid review of the role of JQ1 in Prostate Cancer

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For men in the UK, prostate cancer (PCA) is the number one most common cancer. Although early-stage prostate cancer is curable, in advanced prostate cancer, current treatment is not curative. To increase survival in this cohort, investing in research to find different therapeutic targets is worthwhile in order to give patients a better chance to live. Epigenetics is an emerging field, and in particular, bromodomain and extra-terminal motif (BET) proteins have caught the attention of researchers in a variety of different cancers. Several clinical trials are ongoing to look at the effect of BET inhibitors in a variety of cancers, including prostate cancer. JQ1 is a first-in-class potent inhibitor of the BRD4 signaling pathway which is being widely evaluated in cancer studies.

A rapid review was conducted in a 12-week period undergoing a comprehensive literature search utilizing two online databases: PubMed and Web of Science; in order to evaluate the effects of JQ1 in prostate cancer.

This review found that JQ1 acts by disrupting the BRD proteins from interacting with the androgen receptor (AR), as well as having an effect on the splice variants of the AR. Additionally, JQ1 targets a number of AR target genes including C-MYC, PAICS, FOXO1, NOTCH3, ERG, MANCR, and genes in the Master Regulatory Network. Moreover, *in vivo* mouse models show that JQ1 reduces tumour size, and further *in vitro* work has demonstrated the effects of JQ1 on cell cycle, proliferation, migration, invasion and cell viability, as well as its effects on PDL-1 and the glucocorticoid receptor.

Establishing the Optimal Protocal for Gammadelta T-Cell Immunotherapy Clinical Studies

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Gammadelta (γδ) T-cells are a distinct subgroup of T-cells that have be shown to have a wide range of antitumour effects and the ability to be activated by a number of both naturally derived, such as microbederived HMBPP, and synthetic small molecules, such as Zoledronate. Because of this, they have gained a large amount of interest in the development of novel immunotherapeutic agents against a variety of different cancers. Due to the wide variety of small molecule activators available, a number of different γδ Tcell treatment protocols have been previously investigated. For this reason, a rapid review was initiated using an extensive literature search of PubMed and ScienceDirect in order to optimise the protocol for future γδ T-cell immunotherapeutic clinical trials. The findings of this rapid review highlighted the great variety of treatment methodologies previously used in clinical trials. The majority of published papers used zoledronate infusions and subcutaneous injections of interleukin-2 to activate the γδ T-cells in vivo. However, there is an increasing number of papers that were focusing on activating γδ T-cells in vitro before infusing patients with the T-cells. Similarly, there is an increasing focus on the use of naturally occurring

small molecule activators, specifically HMBPP, to activate γδ T-cells in vitro before infusion into patients. Furthermore, these more recently developed treatment protocols involved fewer or no subcutaneous interleukin injections. By cross-referencing the clinical responses exhibited by patients following the different treatment protocols, it was determined that the use of alternative activators such a prodrugversions of HMBPP elicited a greater response in patients with a greater antitumour efficacy and reduced toxicities. Furthermore, it was concluded that future protocols should involve as few infusions and injections as possible as this results in fewer treatment-related adverse events.

Is there a role for Src kinase in endocrine response and resistance?

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Breast cancer is the most commonly diagnosed cancer in women worldwide. Breast cancer can be classified based on the molecular subtype in luminal, HER2-enriched and triple-negative. The majority of breast cancers highly express the ERa. Treatment for patients with increased ERa levels in endocrine treatment involved hormonal therapy such as the selective estrogen receptor modulators (SERMs), selective estrogen receptor downregulators (SERDs), aromatose inhibitors (AIs) and ovarian ablation. The most widely used hormonal therapy is tamoxifen, which is a SERM. Despite the effectiveness of endocrine therapy, development of resistance is inevitable. Many studies have been reported that the ER-Src axis implicated in the acquisition of tamoxifen resistance. Src is the first identified kinase and a member of the Src family kinases (SFKs), and it has been reported that in breast cancer, its expression and activity are upregulated. A rapid review was conducted over 3 months, using three databases (PubMed, Scopus and Web of Science) in order to investigate the role of Src kinase in endocrine response and resistance in breast cancer.

The findings suggest that Src tyrosine kinase plays a pivotal role in the acquisition of endocrine-resistant through its implication in multiple signalling pathways, such as MAPK and PI3K/Akt pathways.

Sphingosine 1 phosphate receptor 1 in breast cancer

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In the UK breast cancer accounts for more than 30% of cancer cases in women. Subsequently, the need to study and understand this type of cancer, lead scientists into conducting more research with some astonishing results over the years. Some of these discoveries include the involvement of sphingosine 1-phosphate receptor 1 (S1P1) in breast cancer and many studies unravel various complex participation of the receptor in carcinogenesis and have been used in this study. Different databases had been utilised to find literature that met the criteria of the hypothesis and then selection process occurred to verify that the inclusion criteria were met. S1PR1 is a receptor that falls in the GPCR family and when is activated, multiple signals are fired towards different molecules that in turn initiate further downstream pathways. Findings in this review showed that different cancer subtypes along with the stage of the cancer are strongly correlated with S1PR1 overexpression on the membrane of the cells. S1PR1 is actively involved in the angiogenesis and lymph angiogenesis through development of lamellipodia after initiation of VEFG-A pathway. Overexpression of the receptor on TNBC cells is linked with poorer prognosis and decreased overall survival. The metastatic propensity of breast cancer has also been linked with the receptor's overexpression in triple negative breast cancer patients and involvement of S1PR1 with the inflammatory ILL22 receptor. Simultaneous overexpression of S1P1 and S1P3, alongside ERK1/2 is shown to be associated with tamoxifen resistance and decreased overall survival. Numerous antagonists of the receptor have been studied with Fingolimod (FTY720) being first on the list, which potently antagonises S1PR1 and lowers STAT3 activation ultimately sensitizing tamoxifen treated cells. Therefore, further research is required to expand and increase knowledge available to us regarding S1P1 and breast cancer through controlled studies and clinical trials.

Prognostic evaluation of Proteasome complex in a clinical and pathologically distinct cohort

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Glioblastoma Multiforme (GBM) is the most aggressive form of glioma and has a median survival of just 14 months. Current therapies including surgery, radiation and chemotherapy have not improved patient survival. According to earlier studies, it has been found that proteasomes help keep the glioblastoma cells cellular processes functioning smoothly. B subunits of proteasomes are the major functional subunit. The aim of this study was to determine the regulatory role of the β units in primary untreated de novo glioblastoma patients. The bioinformatics approach was chosen to determine this, using the TCGA dataset.

A meta-analysis study was carried out using the online tool Oncomine to retrieve studies involving gene expressions of proteasome β subunits along with the mRNA expression in the GBM population. A list of co-expressed genes was also obtained using Oncomine. Interactions between co-expressed genes were studied using STRING to understand effects of the subunits on other upstream and downstream processes. The findings were validated using survival analysis performed using R2.

Results from the studies suggested that among all the subunits, B5i and β1i showed a potential of prognostication for GBM patients. Concluding the data analysis on immunoproteasome and proteasome expression, gene interaction and survival analysis may reveal new understanding on GBM progression and clinical progression

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Use of Src Kinase Inhibitors in The Endocrine Response and Resistance in ER+ Breast cancer in pre-clinical studies, A rapid systemic literature review

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Breast cancer presents a major clinical issue, in both postmenopausal and premenopausal women . Despite the development of endocrine agents in treating ER+ disease, resistance to this therapy is often inevitably acquired, occurring in up to 40% of patients. Single agent RTK inhibitors such as gefitinib and Herceptin have improved the progression free survival in patients with resistant disease, but due to development of resistance to these drugs current research now draws focus towards Src inhibitors as Src is known to converge from multiple upstream RTK family members that may be present in HR+ breast cancer such as Her2, EGFR, or IGFR. Pre-clinical data, both in-vivo and in-vitro has been analysed in this review selected using PRISMA screening procedures, focussing on studies of luminal A and luminal B cell lines: MCF7, T47D, MDA-MB 361, BT-474 and HCC1248. In this systemic review, studies from primary research papers of high quality standard shows by combining the Src inhibitors (SI), either Dasatinib or Saracatinib with ER inhibitors in cell culture or mouse models that the cells are resensitised to anti-hormone therapy as cell cycle arrest at G1 occurs. This has been depicted from western blot studies were p-Src levels decrease alongside p-ERK or P-MAPK, with simultaneous reduction in % of cells in S phase as indicated by decreases in the cell cycle marker cyclin D1 and increases in P27, with concomitant cell viability in two way approaches of modelling acquired resistance. HCC1248 cells, on the contrary had low p-Src levels so the combined therapy was deemed unsuccessful and stipulated the need for patient cohort stratification when using Src inhibitors and endocrine agents as dual targets. Additionally, data on Src inhibitors in resistant and amenable Triple negative breast cancer cell lines proposes potential progress towards approving SI's as a treatment in the clinical setting.

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

ADCs in clinical trials and receptor-mediated endocytosis: what are we missing?

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Antibody drug conjugates and endocytosis: Is enough known about the mechanisms of internalisation of this novel class of anti-cancer therapeutic?

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Antibody-drug conjugates design: Is endocytosis overlooked?

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Limitations and potential facilitators and benefits of managing chronic conditions in community pharmacy settings

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Pressure on GPs is increasing due to an ageing population with an increased burden of chronic diseases. Community pharmacists (CPs) can potentially help provide healthcare for people with chronic conditions, thereby reducing the burden on GPs. Asthma was chosen as an example of a chronic condition to assess how well it is managed in the current type of practice. A mixed-method approach was used to investigate how well asthma patients were managed and to identify the opportunity for involving community pharmacies more generally in Managing Chronic Conditions (MCCs). The research show that most asthma patients were not well managed (60.9%), did not adequately adhere to their medicines (76.8%), and were not using their inhalers properly (67%). To understand the potential involvement of CPs in MCCs, two qualitative studies and one postal questionnaire project were conducted. Semi-structured interviews were undertaken with CPs and stakeholders of community pharmacy services in Wales. Sixteen individual interviews were conducted: eleven face-to-face and five telephone interviews. Using inductive thematic analysis, strengths of community pharmacy settings, exploiting opportunities to provide a community-based chronic condition management service, barriers, and facilitators to MCCs in community pharmacies were identified. The themes were not only related to community pharmacists/pharmacies but also involve other stakeholders (e.g. patients and healthcare providers) and healthcare system (e.g. policy and regulation). To generalize the qualitative findings to a larger population, a postal questionnaire was designed based on the identified themes, and then disseminated to all community pharmacies in Wales (n=715, response rate=32.8%). The questionnaire survey showed a relatively high level of agreement among respondents to the identified themes. Of the 19 questions, 16 had a percentage agreement of almost 60% or more. Of those, 11 questions had a percentage agreement of 75% or more. In conclusion, although the potential benefit of managing chronic conditions in community pharmacies was recognised, there were several limitations that need to be addressed prior to moving forward.

Potentiation of pomegranate rind extract (PRE) bactericidal activity by $ZnSO_4$ combination

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The addition of Zn(II) to PRE was previously found to increase virucidal activity of PRE by seven log reduction in plaque forming units against Herpes simplex virus. This thesis tested the same system for antibacterial and bactericidal activity against bacteria that are often associated with skin and wound infections. Antibacterial synergistic activity of PRE + Zn(II) was tested using a checkerboard test and showed synergy with MRSA and S. epidermidis with FIC index ≤0.5 and MIC level of PRE in the combination at (62.5, 31.25 µg/mL) and Zn(II) at (1600, 400 µM). In addition, suspension time-kill testing showed synergistic bactericidal activity with PRE 1 mg/mL + ZnSO4 (0.125 and 0.25M). The cytotoxicity of PRE ± Zn(II) was investigated using MTT and FACS analyses, short term exposure showed that PRE (5-50 µg/mL) was tolerated and no significant toxicity on HaCaT cell line was observed. In vitro scratch wound model was investigated and showed that PRE at lower levels mediates HaCaT cell migration compared to untreated group. Significant cell migration mediation was observed with PRE 10 µg/mL and Zn(II) (25-100 µM), as did the combination that contained PRE (5, 10 µg/mL) with ZnSO4 50 µM. Optimization of topical hydrogel formulations resulted in three formulations that showed promising permeation and penetration profiles using in vitro porcine epidermis. Formulations applied to inoculated porcine in simulated in-use conditions again demonstrated syndergistic bactericidal activity of PRE + Zn(II) with >5 log reduction in MRSA inoculated porcine kin after 20 minutes contact time compared to ~1 log reduction for the control.

Development of novel antibacterial agents through the design and synthesis of Aminoacyl tRNA Synthetase (AaRS) inhibitors

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Antimicrobial resistance is a global public health issue which significantly threatens human life. There are approximately 50,000 deaths in the USA and Europe per year owing to antimicrobial resistance infections. This burden of resistance has increased resulting in an increase in morbidity and mortality in clinical and community setting. Thus, global collaborative action is needed for developing effective strategies to combat antimicrobial resistance. International and local approaches including antimicrobial surveillance, guidelines for treatment of bacterial infections, regulation of the availability of antibiotics, improving hand hygiene, understanding the mechanism of bacterial resistance and development of new antimicrobial agents have been advised. Aminoacyl tRNA synthetases are valuable targets for antibiotic development as they have a fundamental role at a cellular level during the translation process of the genetic code. Mupirocin (Bactroban ®) is an approved isoleucine tRNA synthetase inhibitor which is used for the treatment of methicillin resistant Staphylococcus aureus (MRSA). High and low level of mupirocin resistance has been demonstrated in most S. aureus isolates due to acquired plasmid-mediated mupA, which encodes a novel IleRS and mutation, respectively. Thus, the design of multitarget aminoacyl tRNA synthetases inhibitors could be an effective way to make significant reductions in the biological fitness of bacteria leading to a reduction in drug resistant microorganisms. Class IIb aminoacyl tRNA synthetases of which AspRS and AsnRS belong is a target of the project in Staphylococcus aureus and Enterococcus faecalis. A computational study of both enzymes in both microorganisms including homology modelling, validation techniques, molecular dynamics and docking of the natural substrates (aa-AMP) were used to be a platform for the design of dual site inhibitors containing a sulphamoyl linkage which mimic aa-AMP in both enzymes. Different series of AspRS/AsnRS inhibitors were designed to occupy both pockets of the target enzymes then synthesised after optimisation their synthetic routes. The minimum inhibitory concentration of compounds against a panel of microorganisms were evaluated compared with ciprofloxacin as the standard and one compound showed good inhibitory activity against Enterococcus faecalis (MIC = 2 µg/mL).

Design and synthesis of novel CYP51 inhibitors

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Fungal infections are a global issue affecting over 150 million people worldwide annually with 750,000 of these caused by invasive Candida infections. The outcomes of life-threatening systemic infections caused by *Candida albicans* are poor with mortality rates estimated to be between 46-75%. Azole drugs are the frontline treatment against fungal infections however resistance to current azole antifungals in *C. albicans* poses a threat to public health. Azole resistance can arise through several mechanisms with point mutations in sterol 14α-demethylase (CYP51) leading to amino acid substitutions a major contributor. The aim of this research is to design and synthesise novel azole inhibitors effective against wild type and fluconazole-resistance Candida strains. The development of potent and selective inhibitors from three azole series were investigated for CYP51 inhibitory activity, binding affinity, and minimum inhibitory concentration (MIC) against C. albicans strains biologically as well as computationally. The first series, short and extended novel imidazole/triazole derivatives were synthesised successfully. The short derivatives were more potent against the *C. albicans* strains (MIC 0.03 µg/mL) compared with the extended derivatives (MIC 1 µg/mL), while both series showed similar enzyme binding and inhibition (Kd low nM, IC_{50} submicromolar) and were comparable with the standards fluconazole and posaconazole. The short series had poor selectivity for CaCYP51 over the human homolog, while the selectivity of the extended series was higher (21.5-fold) than posaconazole (4.7-fold) based on Kd values, although posaconazole was more selective (615-fold) compared with the extended series (461-fold) based on IC_{50} values. Another extended series (series two) derivatives, were synthesised successfully. The novel inhibitors exhibited weak activity against *C. albicans* strains; however, a slight improvement in the IC_{50} was shown in chloro derivatives (IC_{50} 4.6 -1.3 µM). A final series was synthesised using an efficient synthetic route and shown to be potent against the *C. albicans* strains (MIC from <0.03 to 1 µg/mL) and potent inhibitors of CaCYP51 (IC_{50} 0.78 to 1.6 µM) compared with the standard fluconazole. All series were studied computationally using CaCYP51 crystal structure (PDB 5FSA) for molecular modelling and molecular dynamic simulations to determine optimal fit in the active site and binding interactions. Leishmania was also of interest as it has been identified by the WHO as a disease with unmet needs with an estimated 700,000 to one million

new cases each year in the endemic regions such as East Africa, North Africa and West Asia. CYP5122A1 an orphan enzyme has been identified as a CYP enzyme specific to leishmania, which could provide a novel target in the treatment of leishmania infections. A CYP5122A1 homology model was developed, as no crystal structure is available, using a combination of homology modelling, molecular dynamics simulations, and molecular docking to understand the active site and the binding interaction of CYP5122A1 and selected ligands complexes. Docking results for CYP5122A1 showed amino acids Glu365, Thr366, Val440 in the haem binding pocket and Tyr175, Phe178, Pro441, Asp584 in the access channel, which could have an important role in the binding interactions with designed ligands. Furthermore, some of the novel compounds synthesised in this research were also tested against *Leishmania donovani* to investigate the inhibitory potential.

Development of a multiplex sensing platform for the accurate and rapid diagnosis of sepsis

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Sepsis derives from an uncontrolled response of the host immune system to a pathogenic insult. The complex, rapidly evolving nature of the condition makes diagnosis difficult, and to date a single 'gold-standard' biomarker has not been reported. An increasing number of studies suggest that monitoring of a panel of biomarkers, ideally at point-of-care, is needed. The present study therefore focused on the development of a multiplex biosensing platform targeting lipopolysaccharide (LPS), c-reactive protein (CRP), and procalcitonin (PCT). The study designed a series of electrochemical sensors targeting the three selected biomarkers. Whilst all systems employed aptamers as the recognition element, a hybrid system combining aptamer and molecular imprinting technology was also developed for LPS. Following optimisation of sensor design, electrochemical impedance spectroscopy was used to evaluate performance (binding affinity (Kd), sensitivity, selectivity and dynamic range). Aptasensors were developed for all markers with varying degrees of success. Whilst the optimised aptasensors for LPS and CRP demonstrated good performance, the PCT aptasensor showed poor stability. Despite these issues however, a limit of detection (LOD) of ~ 25 pg/ml was achieved. LODs for LPS and CRP were 100 and 250 fg/ml respectively. The use of a hybrid imprinting approach further enhanced the performance of the LPS detection system, taking the LOD down to 1 fg/ml whilst also increasing binding capacity. Although aptamer-based sensing systems have been described for LPS and CRP, to the best of our knowledge, this is the first report of a such a system targeting PCT. The hybrid imprinting strategy exploited in the study has previously been demonstrated for prostate specific antigen, however this is the first report of such an approach being used for non-protein targets. The recognition of such molecules using conventional imprinting approaches has been largely unsuccessful; the method described herein should be translatable to other biologically relevant targets.

Exploring factors that influence the supply and use of antibiotics from community pharmacies in Thailand

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In Thailand, antibiotics are available lawfully from community pharmacies without a prescription. Inappropriate supply of antibiotics from Thai community pharmacies to the public for common, self-limiting diseases has been reported, and is associated with increased antimicrobial resistance. This study aims to explore factors influencing the use and supply of antibiotics from community pharmacies in Thailand. Semi-structured interviews with Thai community pharmacists (n=23) and citizens (n=21) were conducted to explore the practice and reasons for antibiotic supply from pharmacies. Findings from the interviews and a literature review were used to develop a questionnaire for a stratified sample of community pharmacists, including nine vignettes for pharmacists to identify how they would respond in practice. Approval was obtained from Thailand and Wales ethics committees. Three-hundred-and-twenty community pharmacists in all four Thai regions responded. In response to vignettes, 46% (147/320) of pharmacists would supply antibiotics without an appropriate indication for a URI, 50% (321/638) of pharmacists would suggest inappropriate antibiotics and/or regimens for patients with possible/probable group A streptococcal pharyngitis. In addition, 13% (74/640) and 11% (71/638) of pharmacists would supply antibiotics for acute diarrhea and simple wounds, respectively, where antibiotics were not recommended. Inappropriate antibiotic choices and/or incorrect dosage regimens were also reported.

A higher proportion of younger pharmacists and/or those with less experience, Pharm D. graduated pharmacists, employee pharmacists and those pharmacists who worked in a chain pharmacy were more likely to indicate appropriate antibiotic supply in response to the vignettes ($p<0.05$). Additionally, pharmacists who perceived an advantage of antibiotics is being cured quickly, were more likely to indicate less appropriate supply of antibiotics ($p<0.05$). The findings suggest that improved public education, more pharmacist education on antibiotic use and AMR, better enforcement of existing regulations and stricter regulation on the supply of some antibiotics may lead to improved rational antibiotic use in Thailand.

4th Generation aromatase inhibitors for the treatment of breast cancer: design, synthesis, biochemical and molecular biology studies

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Breast cancer is one of the most common forms of cancer worldwide with 11.6% of all cancer incidence in 2018. One in every eight women will be diagnosed with breast cancer during their lifetime and approximately 70% of all patients are oestrogen receptor (ER) positive depending upon oestrogen for their growth. Oestrogens are synthesised from androgens through three steps, the last of which is catalysed by aromatase enzyme (CYP19A1), accounting for third generation aromatase inhibitors being the mainstay in the treatment of ER-positive breast cancer. Despite the success of current aromatase inhibitors, acquired resistance occurs after prolonged therapy. Although the precise mechanisms of resistance are not known, lack of cross resistance among aromatase inhibitors drives the need for a newer generation of inhibitors to overcome this resistance alongside minimising toxicity and adverse effects. Novel inhibitors including 22 triazole-based compounds and 12 pyridine-based compounds were designed based on previously published parent compounds by our group, making use of the now available crystal structure of CYP19A1 (PDB 3S79), to make modifications at specific sites to explore the potential of dual binding of both the active site and the access channel. Modifications included adding long chain substituents at different positions. The designed compounds were synthesised through various synthetic pathways and were fully characterised to ensure the effectiveness of the methods and quality of the products including the most active compound with IC_{50} value in the picomolar range (0.09 nM). Aromatase inhibition results paired with the molecular dynamics studies provided a clear structure activity relationship and favourable dual binding mode was verified. Also, 11 sulfamate-based compounds were designed by the incorporation of the sulfamate group into the aromatase inhibitors to explore the aromatase/sulfatase dual inhibition. Six of these compounds were based on the triazole scaffold, however biological evaluation revealed no sulfatase inhibitory activity despite the potent aromatase inhibition. Modifications led to the synthesis of the other five compounds to achieve a balanced aromatase/sulfatase inhibition. However, the synthetic scheme for these compounds was not optimal either owing to poor reactivity of starting material and/or questionable purity of the products. This requires more investigation by working with larger scale and/or modifications to the structural design to overcome the low yield produced and the extensive purification process. Proliferation assays and CYP selectivity profile studies for the most active compounds will be performed to select the best candidate for further development and investigations.

PINK1 modulators as novel treatments for Parkinson's Disease

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Since the discovery that loss-of-function mutations in PINK1 result in early onset Parkinson's disease (PD), there has been growing interest in the development of PINK1 activators as potential PD treatments. PINK1 is a serine/threonine kinase that is responsible for stimulating the autophagic removal of toxic, depolarised mitochondria through a process called mitophagy. Mitophagy occurs in many cells including dopaminergic neurons and therefore it has been proposed that by activating PINK1-dependent mitophagy, it would minimise oxidative stress and in turn prevent the loss of dopaminergic neurons that is characteristic of PD. This thesis focused on the design, synthesis and in vitro evaluation of a series of small molecules as PINK1 activators. A few hit compounds were identified that were more potent and less cytotoxic than the reported PINK1 activators.

Role of Caveolin-1 in microglial phenotype: impact on Glioblastoma

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Glioblastoma multiform (GBM) is a lethal brain tumour composed by many distinct cell types that are closely connected and dependent on their surrounding environment. Microglia are the brain immune cells, which are highly abundant in GBM and create an immunosuppressive microenvironment that promotes tumour progression. Caveolin-1 (Cav1) is the most important protein of caveolae and it is involved in cell signalling activity. In the GBM, Cav1 promotes the tumour invasion and it is correlated with a poor prognosis. In immunes cells, its role is not well explored, however it can be involved in immune response. Our hypothesis was that Cav1 could have an impact in the response of human microglia to the environment, influencing tumour progression. To test our hypothesis, a human microglia cell line and an iPSC cell line were used to generate Cav1 knockout clones using CRISPR-Cas9 technology. The iPSC was used to generate human microglia cells. Primary human microglia expressed low levels of Cav1, which could be regulated upon activation. The viral immortalized human microglia cells expressed strong Cav1 protein levels, possibly correlated with the immortalization procedure with SV40 large T antigen. This infection in combination with the culture conditions might lead to a constitutive pro-inflammatory phenotype, impacting the ability of microglia to react to other stimulus and to do phagocytosis. A slightly modified protocol to generate microglia from iPSC allowed the differentiated cells to be polarized towards pro-inflammatory and anti-inflammatory phenotype and to perform phagocytosis. In microglia, Cav1 was involved in the regulation of the inflammatory response, cell migration, phagocytosis, and sensitivity to temozolomide. The microglia cell line did not impact the tumour behaviour, likely due to the profile presented by the cells. However, the deletion of Cav1 in microglia derived from iPSC promoted the tumour invasion.

Catalytic production of hydrogen peroxide for in situ disinfection in medical applications

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Contaminated endoscopes and infections associated with them have been repeatedly reported in the literature. There have been numerous outbreaks and pseudo-outbreaks associated with poorly disinfected endoscopes. Rinse water poses important problems in endoscope disinfection such as recontamination of endoscopes and contamination of patient samples. Biofilms are also a substantial problem for disinfection of endoscopes. The aim of this project was to explore an integrated system based on catalytic technology to produce H_2O_2 to provide sterile rinse water for endoscope reprocessing in automated endoscope reprocessors (AER). The catalytic technology used in this project was based on a gold and palladium catalyst which was tested in batch and flow reactors. Flow reactor treatment was a thousand times more effective at killing *Esherichia coli* K12 JM109 (4 $\log_{10}$ reduction) than 200 ppm of commercial and batch reactor H_2O_2 in suspension (~1 $\log_{10}$ reduction). Moreover, flow reactor treatment with 1% w/w AuPd/TiO2 catalyst was extremely effective against MS2 bacteriophages (8 $\log_{10}$ reduction) while 200 ppm of commercial and batch reactor H_2O_2 in suspension was ineffective (< 1 $\log_{10}$ reduction). Furthermore, 200 ppm of the flow reactor H_2O_2 prevented formation of *E. coli* K12 JM109 and *B. subtilis* ATCC6633 biofilms. H_2O_2 did not play a major role in the microbicidal activity of the catalyst. The proposed mechanism of microbicidal action is that in a H_2/air mixture, H• initiates a cascade reaction turning O_2 into OOH• which can either attack the microorganisms on its own or can propagate radicals. H_2O_2 synthesised in the reactor contributes to support the flux of free radicals out of the surface of the catalyst. Ultimately, the system tested in this project has an innovative mechanism of action and showed a high microbicidal activity. However, further studies on its optimisation are necessary for its incorporation into AER.

Pharmacology of vascular responses to trace amines

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Trace amines including β-Phenylethylamine (β-PEA) and tyramine are vasoactive monoamines closely related to the classical neurotransmitters, noradrenaline, serotonin (5-HT) and dopamine. As vasoactive substances, the trace amines are considered sympathomimetic, eliciting vasoconstrictor responses through noradrenaline release, although they can also induce vasodilator responses. The trace amines are well-known agonists of trace amine-associated receptors (TAARs), of which TAAR1 is expressed in rat aorta. Pharmacological characterisation of TAAR1 has proven difficult as TAAR1 is located in intracellular compartments and is poorly expressed at the cell surface. Previous studies have attributed both trace amine-induced vasoconstrictor and vasodilator responses to TAAR1. The aim of the current thesis was to pharmacologically characterise both the vasoconstrictor and vasodilator actions of the trace amines. β-PEA- and tyramine -induced vasoconstrictor response in rat aortic rings were both significantly potentiated by endothelium removal or inhibition of endothelial nitric oxide synthase (eNOS). Vasoconstrictor responses to β-PEA were found to be resistant to blockade of post-synaptic uptake-2 transporters, antagonists of 5-HT2 receptors, α1-adrenoceptors, D1 and D2-class dopamine receptors and the mouse-specific TAAR1 antagonist, EPPTB. This indicates that β-PEA-induced contractile responses are likely mediated by a currently unidentified cell surface receptor or receptors. As EPPTB, is a poor tool for the study of rat TAAR1, it is possible that TAAR1 located at the plasma membrane mediates these responses. β-PEA-induced vasodilator responses in rat aortic rings were partially attenuated by endothelium removal or inhibition of eNOS. Vasodilator responses to β-PEA were resistant to antagonists of muscarinic M3 receptors, β2-adrenoceptors and EPPTB. β-PEA-induced vasodilator responses were completely abolished by inhibition of uptake-2 transporters indicating that vasodilation is mediated by an intracellular receptor such as TAAR1.

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