Oral abstracts

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Molecular phenomic and systems medicine approaches to healthcare in a COVID-19 dominated world

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Genes, diet, microbes and environment determine our short and long-term health risks and how we respond to therapeutic interventions. These factors also determine metabolic phenotypes that are statistically and biologically linked to disease risks and outcomes. The COVID-19 pandemic will dominate world healthcare for years and the disease causes unique acute and long term health threats. The application of phenomic based systems medicine will be illustrated with respect to the natural history of the SARS-CoV-2 virus interactions with human, tracing the journey from health to disease to long term risks and to address critical questions related to detection, severity prediction, multi-systems failure and to monitoring the recovery or long term impairment to virus exposure.

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Frankenfood and factory farms: Lessons from communicating science in agriculture

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Introduction. Global events in 2020 have made it abundantly clear that providing citizens with accurate and accessible scientific information is a challenging task. Even more challenging however, is motivating sustainable behavioural change in the face of conflicting messages, some of which come from authorities but which, by necessity, are based on incomplete evidence. So how might we communicate science in an age of uncertainty? What lessons can be learned from other domains, such as agriculture, where public knowledge is low, the science is complex, values are socially constructed, and diverse organisations jostle for position as the most credible authority?

Discussion. Initial efforts to communicate about the role of gene technology in agriculture focused on educating the general public about the 'science behind' the development of genetically-modified (GM) foods. This mode of science communication, known as the 'deficit model' was deployed in response to a correlation between low knowledge and negative attitudes found in several studies, and hence the goal was to increase the public's knowledge about GM foods so they would be more accepting of them. For a range of reasons, this approach proved unsuccessful by most measures (Ahteensuu 2012) and although it continues to be a popular approach among scientists (Simis et al 2016) science communication scholars now consider the 'deficit model' ineffective at best at changing public attitudes to a technology. More recently, there have been calls to shift the focus in agricultural science communication practice to areas that influence how people receive and evaluate information, such as trust and trustworthiness. For example, O'Neill (2018) argues that new communication technologies have disrupted our capacity to assess the trustworthiness of communication, and as communicating science in age of uncertainty may need to focus more on 'why' or 'how' we know, rather than 'what' we know.

Ahteensuu M (2012) J Agric Environ Ethics 25: 295–313
O'Neill O (2018) Int J Philos Stud 26(2): 293-300
Simis MJ et al. (2016) Public Underst Sci 25(4):400-414

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Communicating science in an age of uncertainty: The foam and the fury – PFAS and possible risk of cancer

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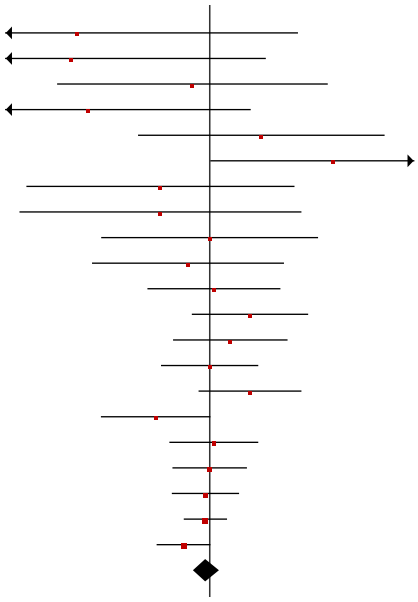
Introduction. The Expert Health Panel on per- and poly-fluoroalkyl substances (PFAS) was convened in 2017/2018 to advise the Australian Government/NHMRC on the potential health impacts of PFAS exposure and identify priority areas for further research. The panel summarised recent scientific reviews by regulatory authorities and systematic reviews.



The conclusions in relation to cancer were identical to those of overseas regulatory agencies. That is, the evidence was very limited in scope (mainly based on one large study on PFOA – Barry 2013 – the Figure shows a Forest plot of the association of 2411 cancers with Ln increase in PFOA exposure – indicating overall hazard ratio for all cancers of 0.99 (95% CI 0.96 to 1.02)). The only concerning signal was a possible increased risk of testicular and kidney cancer, with no human evidence that supported an overall risk of cancer.

In contrast, the press on PFAS (including on this report) has been dominated by sensationalist headlines on the toxic effects, and in particular cancer, anecdotes from victims and outraged communities, and promotion of class action lawyers.

In 2020, a $212 million dollar settlement was reached with the three communities most affected – after the lawyers took their cut this was reduced to $126 million. The payout was calculated entirely based on financial losses such as damage to property values. However, presumably the public wouldn't have guessed this when they'd read the Sydney Morning Herald headline: "Court links toxic foam to cancer in legal blow to government". Clickbait beat acknowledgement of uncertainty, for the umpteenth straight occasion.

References. Buckley N, Sim M, Douglas K, Håkansson H. Expert Health Panel for PFAS, Report for the Minister of Health. 2018. 446p. t https://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-expert-panel.htm.
Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect 2013;121:1313–1318; http://dx.doi.org/10.1289/ehp.1306615

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Communicating vaccine risk in the age of COVID-19, lessons from communicating toxicological fears to vaccine refusers)

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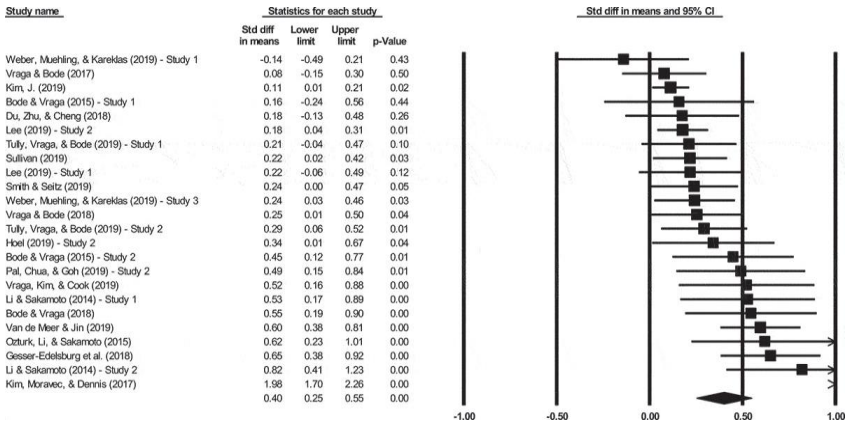
Introduction. "A lie can travel around the world while truth is getting its boots on". The COVID-19 pandemic has seen not only a viral epidemic but an "infodemic" as well, with social media platforms allowing the wide spread of misinformation about the pandemic and its treatments. The development of an effective vaccine will be imperative for combatting COVID-19, however, while we have as yet no vaccine fears about the vaccine(s) have circulated with people already stating they will not take the vaccine.

Many of these fears are based on toxicological concerns, given that the front runners are using new technologies. What can we do to combat these fears and what can we learn for previous experience with vaccine refusal? While an Information Deficit Model, where people are given facts to counter a supposed lack of information, would seem the most intuitive approach, this approach often performs the worst in countering vaccine refusal. Other approaches include "Disease risks", simply listing the risks of contracting the disease, "Disease narrative", telling a "true story" of a child contracting disease and "Disease images" (self-explanatory). Most of these were not very effective.



The good news is that many approaches do have some effect (see figure from Waler et al (2020)). Context, sources of misinformation and the personal involvement of the audience are all factors that inform both the type approach and the success of the chosen approach. The one thing that is clear is that simply talking as an expert from "on high" is not an effective approach.

Nyhan B et al (2014) Pediatrics 2013-2365
Walter N et al (2020) Health Commun 1-9

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Communicating quality use of medicines during COVID-19

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The COVID-19 pandemic has highlighted complexity and challenges in scientific communication. Almost everyone had opinions and shared them. Early on, the media were more agile (supported by social media) than scientific and professional agencies at distributing opinions about new data. These reports are likely to have influenced the opinion of the public and healthcare workers and it is difficult for either group to remain abreast of the latest data, especially when studies report conflicting findings for the same intervention. In this age of media grabs and tweet-sized reporting, the context of new data and relevance to clinical decision-making is rarely made clear to readers.

The COVID-19 era has been a challenge for those committed to the quality use of medicines. The clinical severity of COVID-19 increased angst and confusion. Doing something (eg prescribing a drug) was considered by some to do be preferred to doing nothing. Yet, in many cases the treatments being discussed were not without some risk and the data supporting any benefit were very low quality.

The Australian National COVID-19 Clinical Evidence Taskforce was established to publish 'Living Guidelines' which are evidence-based clinical guidelines updated weekly with the latest research) was useful. These guidelines facilitate the communication of evidence that is locally appropriate at a faster rate than usually possible through peer reviewed journals. The recommendations are communicated using guidance from the GRADE group.

The GRADE group (Grading of Recommendations Assessment, Development, & Evaluation) develops tools for summarising evidence, and wording of the recommendations. GRADE highlight the importance of both the content and method of presentation of recommendations and they separate the quality of evidence from the strength of a recommendation. GRADE provides specific guidance for terminology used for strength of the recommendation (eg "we recommend" or "we suggest") with the level of evidence (eg "high" to "very low"). This incorporates both expert opinion and the quality of the data.

https://covid19evidence.net.au/#living-guidelines

https://www.gradeworkinggroup.org/

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Structure and dynamics of class B1 G protein-coupled receptors

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G protein-coupled receptors (GPCRs) are the largest family of cell surface drug targets. Consequently, there is high interest in understanding the structure of members of this receptor superfamily and molecular detail of how ligands and transducer proteins interact with the receptors. While x-ray crystallography has been the mainstay for GPCR structure determination, this method requires modification of receptors to limit flexibility and to enable crystal packing, and has been refractory to capturing fully active, transducer (G protein) complexed receptor structure. Our laboratory has been applying single particle cryo-EM to determination of active GPCR structures, using minimally modified receptors. We have now solved >50 structures of 17 unique receptors, with a focus on class B1 peptide hormone GPCRs; many at high resolution (<2.5 Å). Moreover, unlike x-ray crystallography that captures a single receptor conformation, cryo-EM can access the spectrum of conformations present during vitrification allowing 3D reconstruction of conformational dynamics of GPCR complexes along principal components. This new insight into receptor dynamics has been critical to understanding differences in the pharmacology of different ligands that can interact with the same receptor or receptor family.

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Discovery and development of novel amylin agonists for obesity and diabetes

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Amylin is a pancreatic peptide hormone that controls blood glucose and body weight. One amylin mimetic, pramlintide (Symlin), is approved for clinical use for insulin-requiring diabetes but there is substantial scope for improvement by developing other amylin mimetic peptides with improved solubility and extended half-life. Amylin receptors are G protein-coupled receptors (GPCR) but are unusual in that they require accessory proteins, in addition to the core GPCR, to bind amylin with high affinity. Specifically, amylin receptors comprise the calcitonin receptor (CTR), together with receptor activity-modifying proteins (RAMPs). The three RAMPs with CTR form the AMY_1, AMY_2 and AMY_3 receptors, respectively. There are several splice variants of the CTR, and thus there are a large number of amylin receptor subtypes that could contribute to the mechanism of action of amylin. This presentation will outline the pharmacology of amylin receptors, their signalling and what is currently known of how amylin binds and activates its receptors. Challenges with understanding where amylin and its receptors are expressed will be highlighted, as this is crucial for designing receptor subtype-selective drugs. Progress towards the development of novel amylin mimetic peptides will also be discussed.

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Fluorescence imaging of peripheral nerves by a $Na_V1.7$-targeted inhibitory cystine knot peptide

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Nerve injury is a debilitating condition that more than 20 million Americans live with. Around 25% of nerve injuries arises from surgery and especially during cancer surgery when the tumour tissue surrounding the nerve is distorted. The voltage-gated sodium channel subtype $Na_V1.7$, the target for many venom-derived disulfide-rich peptides, has actively been pursued for its involvement in pain, is located on peripheral sensory neurons which are susceptible to injury during surgery. Through fluorescent labelling of peptide Tsp1a, a potent $Na_V1.7$ inhibitor from the *Thrixopelma sp*. spider, we can selectively 'light up' peripheral nerves at a non-active dose and without side effects (Gonzales et al 2019). This research could potential result in the use of spider-peptides as nerve-imaging agents resulting in fewer nerve injuries during surgery.

Gonzales J, et al (2019) Bioconjug Chem. 30:2879-2888

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Unique mechanisms of GPCR biased signalling by a peptidomimetic agonist of the relaxin receptor RXFP1

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The peptide hormone relaxin activates the GPCR relaxin family peptide 1 (RXFP1) receptor. Relaxin has demonstrated considerable promise as a treatment for cardiovascular disease and fibrosis. While it did not meet primary endpoints in a Phase IIIb study in acute heart failure, patients showed improvements in markers of cardiac, renal and hepatic damage consistent with the prevention of organ damage. Relaxin is an insulin-like two chain peptide which is not orally active and has a short in vivo half-life necessitating intravenous infusion. Hence the development of peptide mimetics or small molecule agonists is advantageous especially for chronic treatment. Consequently, modified relaxin analogs and small molecules targetting RXFP1 are undergoing continued development by numerous pharmaceutical companies. However, we have shown that relaxin-mediated RXFP1 activation involves multiple ligand-receptor interactions (Hoare et al, 2019) and conformational changes resulting in the N-terminal RXFP1 LDLa module activating the receptor as a tethered ligand (Sethi et al, 2016). This complex activation mode makes the development of mimetics that exactly mimic the mode of relaxin activation challenging. In line with this, we recently developed a relaxin mimetic peptide, B7-33, and showed it has cell-specific actions (Hossain et al, 2016) and have demonstrated that small molecule agonists are biased ligands (Kocan et al, 2017). Our most recent studies utilizing cell based highly sensitive Nanoluciferase-based BRET signalling sensors show that B7-33 is a biased agonist. These kinetic signalling studies demonstrate that low affinity B7-33 binding strongly activates G_i mediated signalling pathways while poorly activating G_s signalling and cAMP activation. This presentation will discuss the mechanism of biased signalling by relaxin peptidomimetics and the challenges of mimetic design for complex peptide GPCR targets like RXFP1.

Hoare BL, Bruell S, Lew MJ et al (2019) iScience 11: 93–113.
Hossain MA, Kocan M, Yao ST et al (2016) Chemical Sci. 7: 3805-3819.
Kocan M, Sarwar M, Ang SY et al (2017) Scientific Reports 7: 2968.
Sethi A, Bruell S, Patil N et al (2016) Nature Comms. 7: 11344.

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Rational design of resistance resistant anti-tuberculosis drugs

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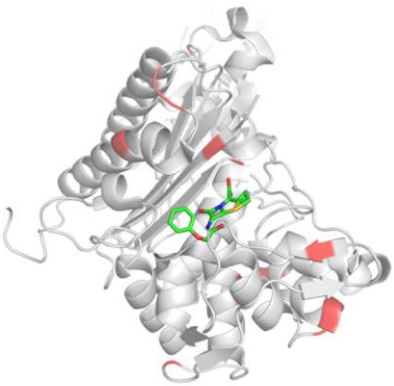

Drugs against infectious disease pathogens (viruses, bacteria and parasites) have transformed human health and saved millions of lives. Nevertheless, their widespread use (and misuse) has led to the emergence of antimicrobial resistance (AMR) that poses a real catastrophic threat to public health. This has been further complicated by the slow rate of introduction of new antimicrobials, with bedaquiline the first anti-tubercular drug with a new mechanism of action in 40 years, and the rapid pace with which resistance can spread.

We have developed a comprehensive computational platform that uses information of the effect of mutations on protein structure and function in order to pre-emptively identify potential resistance mutations before they become fixed in the population. Our initial efforts have focussed on the identification of resistance against the front-line drugs pyrazinamide and rifampicin, and the last line treatment bedaquiline. These approaches are now being used to help guide genomic based patient management and public policy.

The ability to pre-emptively identify potential resistance mutations also has large implications for drug development- by avoiding resistance hot-spots, we can increase the fitness cost associated with the emergence of resistance. In conjunction with our tools for improved computational drug screening and pharmacokinetic optimisation, we have applied this approach to two ongoing drug-development efforts. Identification of resistance hot-spots within the targets guided medicinal chemistry design of inhibitors that remained effective even in extended *in vitro* TB resistance screening assays.

This work has highlighted the potential of using computational and structural insights early in the drug development process. These computational tools are freely available (http://biosig.unimelb.edu.au/biosig/tools), and are being translated in the fight against other infectious and non-infectious diseases.

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Therapeutic drug monitoring in tuberculosis

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Tuberculosis (TB) remains a major global concern. The solution to eliminate TB is multifactorial but treatment optimization is key as both preventative and curative treatment are long and adverse drug effects are common. The introduction of pharmacokinetic and pharmacodynamic science to increase efficacy and reduce toxicity will have an impact on how treatment regimens will be designed. In this presentation the importance of pharmacokinetics and pharmacodynamic (PK/PD) on efficacy of antimicrobial treatment and acquired drug resistance will be presented. The role of PK/PD in the development of dosing strategies and therapeutic drug monitoring has increased and since recently therapeutic drug monitoring has been included in treatment guidelines for TB [1,2]. As implementation of therapeutic drug monitoring in daily practice and programmatic TB treatment is a challenge innovative approaches like limited sampling strategies, point of care tests and dried blood spot analysis will be presented [3].

Nahid P, et al. Clin Infect Dis. 2016 Oct 1;63(7):e147-e195
Nahid P, et al. Am J Respir Crit Care Med. 2019;200(10):e93-e142
Alffenaar JWC, et al. Clin Infect Dis. 2020 Apr 10;70(8):1774-1780

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Bromodomain proteins as potential malaria drug targets

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Introduction. Emerging resistance to existing anti-malarials demands the discovery of new anti-malarial drugs. Novel anti-malarial targets are a priority to reduce the risk of cross-resistance. Bromodomains bind acetylated lysines, often on histones, and typically they recruit enzymes or transcriptional co-factors to chromatin where they participate in gene regulatory processes. Human bromodomain proteins have been pursued as drug targets for multiple diseases and several inhibitors are in late stage development. *Plasmodium falciparum* has seven novel bromodomain proteins (PfBDPs) unique to apicomplexan parasites and one that is conserved in eukaryotes but which carries a divergent bromodomain. We propose that these PfBDPs could furnish novel anti-malarial drug targets.

Aims. We aimed to validate the PfBDPs as anti-malarial drug targets and establish cell based assays to screen inhibitors.

Methods. We used CRISPR cas9 reverse genetics to create inducible knockout/knockdowns (KO/KD) of the PfBDPs and tested these for essentiality in blood stage malaria. We further assessed the function of PfBDPs by dissecting their roles in asexual growth and by characterising their associations with gene regulation. We used our KO/KD parasites to establish inhibitor assays and established a hit validation pipeline.

Results. Three PfBDPs are essential for asexual parasite growth, one is required for normal growth and two are not required for normal growth. The PfBDPs have diverse and overlapping genomic distributions and functions, with two involved in directly activating genes and three involved in chromatin structure regulation. Multiple PfBDPs are involved in critical processes including the tightly coordinated expression of proteins involved in erythrocyte invasion and sexual development. An assay for screening potential inhibitors using tunable KD and over-expressing parasites was established as was a pipeline for confirming target specificity.

Discussion. These results validate multiple PfBDPs as novel anti-malarial drug targets and establish proof of principle cell-based assays for screening focussed sets of compounds for specific inhibition of *P. falciparum* growth via PfBDP inhibition.

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Interprofessional Student-led Influenza Vaccination Clinic

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Introduction. In 2019 we developed a vaccination training course for pharmacy students. Using a modified version of this course we conducted an interprofessional learning activity (IPA) to train medical, nursing and pharmacy students to administer influenza vaccines. We then conducted the first Australian interprofessional student-led influenza vaccination clinic where the trained students, under supervision, administered influenza vaccines in April and May 2020 to health care students prior to their clinical placements.

Aims. To evaluate the IPA from the students' perspectives, and the experiences of those who received vaccinations.

Methods. Students participating in the IPA were invited to complete pre- and post-course surveys,[1] and pre- and post-clinic Readiness for Interprofessional Learning Scales (RIPLS - adapted tool).[2] Both surveys utilised a 5 point Likert scale and open-ended responses to assess the students' perceived current knowledge of influenza and influenza vaccination, their skill and confidence to administer influenza vaccine, and their attitudes to interprofessional learning. Students who received the vaccine were asked to complete a survey on their experience. All data was statistically analysed by using SPSS 24.

Results. There were significant increases in the trained students' perceived knowledge of influenza vaccinations (27% increase, $p< 0.001$), their confidence to administer influenza vaccines (46% increase, $p< 0.001$) and their professional identity (8.9%, $p=0.02$). 543 influenza vaccines were administered in the clinic. 97.1% students vaccinated said they were satisfied/very satisfied with the clinic and 92.4% were very likely to recommend the clinic to other students.

Discussion. Participants welcomed the opportunity to learn and work with students from other health professions. The interprofessional training significantly increased students' knowledge, skills and confidence in administering vaccines. Vaccination training and clinic implementation could contribute to future clinical experiential learning. We have demonstrated that an interprofessional vaccination training program and student-led clinic is effective in providing a vaccination service to university students, and could be used in the future for a coronavirus vaccine.

Carroll, PR et al, Curr Pharm Teach Learn, 2020, 12, 850; doi.org/10.1016/j.cptl.2020.02.016
https://nexusipe.org/informing/resource-center/ripls-readiness-interprofessional-learning-scale

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Learning on the run – Pharmacy educators' experiences with the Australian Pharmacy Residency Program

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Introduction. A residency training program for early career hospital pharmacists was introduced by the Society of Hospital Pharmacists of Australia (SHPA) in Australia in late 2016, modelled on similar programs in other countries. Hospital pharmacy educators are tasked with its implementation and delivering it to pharmacy residents, shaping their learning in the structured workplace training program.

Aims. This qualitative study explored pharmacy educators' early experiences with the implementation of the SHPA pharmacy residency program.

Methods. Two focus groups and two semi-structured interviews were conducted with educators from ten residency sites. Audio recordings were transcribed verbatim and analysed using a mix of deductive and inductive thematic analysis.

Results. Fourteen pharmacy educators and clinical pharmacists involved in implementing and delivering the pharmacy residency program participated in this study. The following themes were developed: Pharmacy educators agreed and focused on the "benefit of structured workplace training", "designated opportunities to perform advanced practice roles" and "readiness of learners".

Discussion. Educators involved in the SHPA residency program identified how the training of pharmacy residents links to both workplace training and adult learning theories. The structure and activities of the program ensure pharmacy residents develop conceptual and procedural knowledge through structured rotation, repeated tasks, regular feedback from supervisors and peers. The enhanced opportunities to advanced practice roles such as conducting research and participation in committees support the development of residents' professional identity by extending their dispositional knowledge. The educators perceived residents' advancement in practice depends on their level of engagement in the program and how they interpret, reflect on and integrate feedback, and residents taking responsibility for their learning.

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How do consumers interact with pharmacy students in educational settings? - A systematic review

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Introduction. Consumers are increasingly involved in the education of healthcare students. Within pharmacy education, consumers may play important roles in teaching students about various medical conditions and practicing communication skills; however, the nature and extent of their involvement has not been explored previously.

Aims. To systematically review the literature relating to the active involvement of consumers in pharmacy education within educational settings.

Methods. EMBASE, MEDLINE, ERIC, IPA, PubMed, PsycINFO, CINAHL and Scopus databases were searched from inception to April 2020 for English, peer-reviewed primary research publications. Searches involved two concepts relating to pharmacy education AND consumer/patient involvement. Studies exploring the active involvement of consumers in pharmacy education within educational settings were included. The aims, type and description of the studies; the nature of student and consumer involvement; and the student and/or consumer outcomes were extracted. Quality assessment was conducted using the Mixed Methods Appraisal Tool.

Results. Twelve articles were included. Nine studies involved consumers educating students about their lived experience and four studies involved consumers as simulated patients. Most consumers were involved in mental health education for pharmacy students (n = 8). Studies which reported on student learning outcomes indicated improvements in knowledge, attitudes and confidence but presented no evidence of the long-term impact of consumer involvement. Among consumers, their involvement led to greater personal satisfaction, empowerment and knowledge from sharing their personal experiences, however, no studies reported on the impact of their involvement on clinical outcomes

Discussion. Consumer involvement in pharmacy education improves confidence, communication skills and knowledge among students, especially within mental health education. Consumer involvement also benefits consumers who value their contribution to education of future health care professionals and to share their lived experience. Further research is required to determine the long-term impact of consumer involvement for both consumers and students, as well as, any potential effects on clinical outcomes among consumers.

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Preparation for practice – Implementation of an e-Bootcamp interactive prescribing series of workshops for final year medical students

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Introduction. Data from the Australian Medical Council Preparedness for Internship survey 2019 found recent medical graduates from all Australian institutions consistently identify prescribing as the clinical task they are least prepared for in practice. Increased practical teaching in various clinical contexts are recommended. In preparation for the new Assistants in Medicine roles within NSW Health, the Sydney Medical Program developed a 2 day e-bootcamp that included a 2 hour interactive prescribing workshop to be delivered via zoom video teleconferencing in April and May. The aim of this study was to determine the impact of the e-Bootcamp prescribing workshop on student confidence in prescribing and to identify areas in which students required further pharmacology teaching.

Methods. A flipped learning approach was used to deliver the two-part workshop in practical prescribing. An online video on medication safety and introduction to prescribing accompanied a complex clinical scenario of an elderly patient with comorbidity, allergies and polypharmacy presenting to ED with COVID19 symptoms (e.g. community acquired pneumonia). Students were asked to review the clinical presentation and complete the prescription of new and regular medications on an electronic medication chart which was uploaded for review in Canvas within 7 days. All medication charts were reviewed, individual and cohort feedback were prepared within 3 days and an interactive workshop discussing safe and accurate prescription and rationale for prescribing was held via zoom.

Results and Conclusion. All Year 4 medical students (n=280) completed a medication chart. 82% of students rated the prescribing workshop as improving their confidence in prescribing. Common errors in prescribing were identified; allergy v adverse drug reaction misidentification (38%), incorrect antibiotic selection due to inaccurate assessment of disease severity (72%), incorrect dose of anticoagulant (48%), inconsistent analgesic prescribing (32-48%), and continuing medications that should be ceased due to deteriorating clinical state (26-38% depending on drug). Student qualitative feedback strongly supported the prework + interactive format for online teaching in prescribing. Further prescribing workshops are planned based on feedback to enhance prescribing skill development prior to internship.

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Can multiple choice questions examine application of knowledge in online assessments?

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Introduction. Due to the unique COVID-19 challenges, Australian universities have transitioned to remote teaching and learning in Semester 1 2020, as the Australian health and foreign affairs authorities implemented social distancing policies, including suspension of all in person class-room activities. Online assessments become obliged and fundamental during this transition.

Aims. The aim of this study is to investigate the use of online multiple choice questions (MCQs)-format assessments to examine the application of knowledge and compare the results with previous years' invigilated assessments.

Methods. MCQs were developed and ranked into one of two cognitive levels, based on a modified Bloom's taxonomy, as knowledge recall 'KQ' or application of knowledge 'AQ'. Ranked MCQs were included in the mid-semester test and final exam of the Veterinary Pharmacology course, then administered to 1st year Doctor of Veterinary Medicine (DVM) students. Student performance on MCQs was compared between and within each Bloom's level throughout the Pharmacology course in 2020, and to previous years. The differences in the percentage of students who obtained a correct answer for each level were then analysed using Student's *t* Test.

Results and Discussion: A total of 58 DVM students were enrolled in the Pharmacology course in 2020. Ninety five MCQs (comprised of 37 KQ and 58 AQ) were included in the final exam and forty MCQs (comprised of 12 KQ and 28 AQ) were included in the mid-semester test. The overall average MCQ score on the final exam was 88.0% and that for the mid-semester test was 85.2%, which were approximately over 10% higher compared to previous years. Student performance on KQ MCQs was consistently higher compared to student performance on AQ MCQs in both assessments, with mean average score of 97.5% compared to 87.0% for the final exam ($p = 0.12$), and 92.1% compared to 85.9% for the mid semester test ($p = 0.28$). Overall, student performance on online MCQs test and exam in 2020 appeared to be consistently shifted to over 10% higher score across all Bloom's level MCQs as compared to previous years invigilated exams. This finding was not unexpected, as online assessments are practically open book exams and students have access to learning material while sitting the exam.

Conclusion: In summary, well-designed MCQs which target various cognitive levels can be used in online pharmacology test and exam to facilitate assessment of student performance in a vet pharmacology course.

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Effect of phenethyl-isothiocyanate on human breast cancer cells MDA-MB-231 and MCF-7

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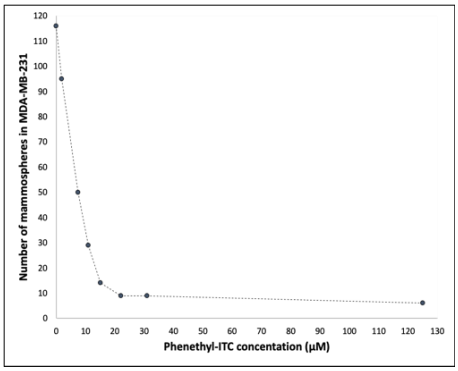

Introduction. Cruciferous vegetables are a rich source of isothiocyanates (ITCs). There has been increasing research interest in the role of different ITCs as these constituents have been found to possess distinct anti-cancer properties. Among the main ITC constituents, phenethyl-ITC has been reported to be protective against breast cancer, however limited data exist on whether this compound also inhibits breast cancer stem cells (CSC).

Aims. This study aims to examine the anti-proliferative effect of phenethyl-ITC against human breast cancer cell lines MCF-7 (estrogen receptor positive) and MDA-MB-231 (triple negative) and whether it can inhibit self-renewal or indeed kill the breast CSC subpopulation within these cell lines.

Methods. To this end, we generated transgenic breast cancer cell lines in which CSC-like cells were marked by expression of a green fluorescent protein (GFP) reporter gene driven by the human Oct4 promoter utilising a mammosphere formation assay.

Results and Discussion. Phenethyl-ITC reduced viability of transgenic breast cancer cell lines with an 50% inhibitory (IC_{50}) value of 5.48 µM for MCF7, and 5.61 µM for MDA-MB-231. These results are consistent with that reported in the literature (Gutpa 2012). Phenethyl-ITC was also found to inhibit the formation of breast CSC mammospheres, with a decrease in mammospheres' size and number in both cell lines, although there is potential that the breast CSC may become quiescent rather than being killed. This speculation was based on our further analysis of CSC markers including the pluripotency gene SOX2, and EMT and drug resistance genes (SLUG, VIMENTIN, DNER, and ABCG2) by qRT-PCR, which did not show a clear dose-dependent response to phenethyl-ICT concentrations.

Conclusion. Phenethyl-ITC displayed the ability to suppress the growth of CSC in MDA-MB-231 and MCF-7, however the non-dose dependent response of CSC markers requires further investigation to define mechanisms involved.

Gutpa et al (2012) BMC Med 10:80.

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Androgen regulated UDP-glucuronosyltransferases (UGT) 2B11 and 2B28 are prognostic indicators in luminal androgen receptor positive/molecular apocrine breast cancer

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Introduction. Androgen receptor (AR) is expressed in up to 80% of breast tumors and androgens promote growth in some ERα-negative (AR^+/ER^-) subtypes. Androgen signaling is irreversibly terminated by androgen glucuronidation. Three UGT enzymes, UGT2B15, 2B17 and 2B28, have been linked to androgen signaling. UGT2B15 and 2B17 catalyze androgen glucuronidation, however UGT2B28 shows no such activity and its function in androgen biology has been enigmatic. Here we define the regulation and function of UGT2B28, and its paralog UGT2B11, in breast cancer.

Aims. 1. To determine the role of the poorly characterized UGT2B28 and 2B11 enzymes in breast cancer outcomes. 2. To define how these UGTs are regulated by androgens in breast cancer

Methods. Comparative expression of UGTs in breast cancer subtypes and associations with survival outcomes were defined using METABRIC data. The mechanism of UGT regulation by androgens was determined in breast cancer cells via qRTPCR, reporter assays, and ChIP. Functional studies used stable gene overexpression and activity assays.

Results. Analysis of data from >2000 breast cancer samples showed that expression of UGT2B28 and UGT2B11 was significantly elevated in AR-positive, ERα-negative and HER2-positive tumors, a set that largely defines the androgen-driven molecular apocrine subtype. UGT expression correlated robustly with AR but not ERα expression. Higher expression of both UGTs correlated with significantly worse overall survival in all ERα-negative tumors, and also in tumors designated by molecular phenotyping as Integrative Cluster 2, which are clinically aggressive and do not respond to neoadjuvant chemotherapy. Both UGT genes were potently induced by androgens in AR-positive breast cancer cell lines, and functional AR and FOXA1 binding sites were identified in the proximal promoters, as well as distal enhancers. Overexpression of either UGT in a AR+/ER- breast cancer cells increased proliferation, consistent with their clinical association with poorer outcomes in this context. Mechanistically, UGT2B11 and UGT2B28 could function to reduce androgen glucuronidation by other UGTs (e.g. UGT2B15 and 2B17) thus facilitating androgen-driven growth.

Discussion. We define two previously enigmatic UGTs as androgen-regulated factors that can drive breast cancer progression, prompting their further investigation as possible therapeutic targets in aggressive, hard to treat tumors.

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A preliminary study on the anti-melanoma effect of novel resveratrol nanoparticle formulations

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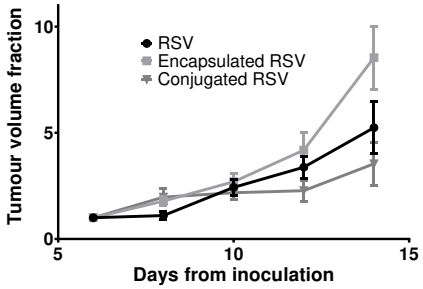
Introduction. Resveratrol (RSV) is a natural plant extract proposed to have anticancer effects. However, due to its molecular structure, it undergoes rapid metabolism in the body resulting in very low bioavailability and poor anticancer effect in vivo.



Aims. In order to improve RSV's anticancer activity, we developed a conjugation strategy to increase bioavailability of RSV via reduction of its metabolism by synthesising novel polymeric RSV conjugates and formulating into nanoparticles (NP) using nanotechnology. We evaluated RSV-conjugated NP alongside free RSV-encapsulated NP as a comparison for anti-melanoma properties *in vitro* and *in vivo*.

Methods. Both RSV-conjugated and -encapsulated NP were assessed for *in vitro* stability against plasma esterases in rat plasma and for phase II metabolism using human microsome using HPLC analysis. NP were then evaluated in a B16F10 (murine melanoma) cell line using the tetrazolium dye MTT for anticancer properties. Following that, NP together with free RSV, were then further assessed in mice bearing subcutaneous B16F10 tumour cells *via* intraperitoneal administration and tumour volumes were recorded every alternate day for 1 week.

Results and Discussion. MTT assays show a better anti-proliferative effect with the RSV-encapsulated NP (25% cell viability) than the RSV-conjugated NP (96% cell viability) at 20 μg/mL RSV equivalent. In the mouse model, the RSV-conjugated NP showed a 33% improvement in suppression of tumour growth compared to mice treated with free RSV, possibly due to its better bioavailability *in vivo*. This correlates with previous data from *in vitro* stability studies against metabolism in human microsomes where free RSV and RSV-encapsulated NP degraded by 50% within 40 minutes as opposed to RSV-conjugated NP within 1 hour. This study suggests that chemical conjugation of RSV to an appropriate amphiphilic polymer is a good strategy to improve the therapeutic effectiveness of RSV for melanoma treatment by reducing metabolism of RSV in mice.

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Triple negative breast cancer: Screening for the invasion amplifying cAMP-calcium feedforward loop mechanism

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Introduction. Previously, we identified a cAMP-calcium (Ca^{2+}) feedforward loop mechanism in the highly metastatic triple negative breast cancer (TNBC) tumour cell line MDA-MB-231^{HM} (Pon et al, 2016). This mechanism facilitates the dynamic interplay between cAMP and Ca^{2+} second messenger systems following β_2 adrenoceptor activation, to further amplify both signals. Activation of this mechanism facilitates accelerated invasion in MDA-MB-231^{HM} cells.

Aims. To determine the commonality of the β_2-adrenoceptor mediated feedforward mechanism amongst a panel of TNBC tumour cell lines and to establish its role in regulating cellular invasion.

Methods. Formoterol was used to activate the endogenously expressed β_2-adrenoceptor. Receptor signalling was measured using cAMP accumulation and Ca^{2+} mobilisation assays in the presence of various inhibitors: adenylyl cyclase (2',3'-dideoxyadenosine), $G\alpha_{i/o}$ (pertussis toxin), $G\beta\gamma$ (gallein), protein kinase A (KT5720), exchange protein activated by cAMP (ESI-09), protein kinase C (GF109203X), and Ca^{2+} chelator (BAPTA-AM). 3D cellular invasion was assessed using microscopy.

Results. Preliminary screening identified three TNBC cell lines which possess elevated cAMP and increased intracellular Ca^{2+} in response to β_2-adrenoceptor stimulation by formoterol; MDA-MB-453 (pEC_{50} cAMP 8.42 ± 0.25 , Ca^{2+} 7.74 ± 0.27), HCC1806 (pEC_{50} cAMP 8.39 ± 0.04, Ca^{2+} 8.70 ± 0.89), HCC1395 (pEC_{50} cAMP 7.97 ± 0.23, Ca^{2+} 8.76 ± 0.51). These results provide preliminary evidence for a cAMP/Ca^{2+} feedforward loop mechanism within these cell lines. Inhibitors were used to delineate any interaction between the cAMP and Ca^{2+} signalling pathways, and to confirm whether activation of the cAMP/Ca^{2+} feedforward loop was required to accelerate invasion.

Discussion. The β_2-adrenoceptor can accelerate breast cancer progression in response to stress. The feedforward loop may provide strategies to more specifically target this GPCR in order to slow cellular invasion and metastasis.

Pon CK et al (2016) FASEB J 30:1144-1154

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The role of UGT enzymes as novel modulators of lipid biosynthesis and SREBP signalling in breast cancer

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Introduction. Elevated lipogenesis is a hallmark of cancer, often caused by an increase in the activity of the master regulators of lipid biosynthesis; sterol regulatory binding protein (SREBP) transcription factors. UDP-glycosyltransferases (UGTs) are a superfamily of enzymes that conjugate sugars to small lipophilic molecules including endobiotics, xenobiotics, and drugs. The expression of two UGTs that have poorly defined activities, UGT2B11 and UGT2B28, has been linked with pathogenic features of breast and prostate cancer. Analysis of the Cancer Genome Atlas Breast Cancer RNAseq dataset correlated expression of these UGT with genes involved in SREBP-mediated lipogenesis. Guided by this finding we investigated functional linkages of UGTs with SREBP signalling in cancer.

Aims. To define the roles of UGT2B11 and UGT2B28 in the regulation of SREBP-mediated lipogenesis.

Methods. UGT2B11 and UGT2B28 variants were stably expressed in MDA-MB-453 breast cancer cells. Cellular proliferation was assessed via crystal violet assay and SREBP lipogenic target gene expression was quantified by qPCR. UGT2B11 and UGT2B28 were transiently co-expressed with components of the SREBP signalling complex in a HEK-293T cell model. The stability of nuclear SREBP protein was assessed via immunoblotting and changes in SREBP transactivation function was quantified using luciferase reporter assays.

Results. Stable overexpression of UGT2B11 and UGT2B28, including active full-length forms and catalytically inactive truncated variants, promoted breast cancer cell proliferation. Gene expression analysis revealed increased levels of multiple SREBP target genes in the UGT-overexpressing cells. Co-expression studies in HEK-293T cells showed that these UGTs can enhance proteolytic turnover of nuclear nSREBPs, leading to reduced transactivation activity.

Discussion. Expression of UGTs appears to enhance SREBP-mediated lipogenesis and proliferation in breast cancer cells. This may involve modulation of the ER-based lipid sensing process that controls nuclear trafficking of SREBP, likely via a non-catalytic mechanism as truncated and full length UGTs had similar effects. The ability of these UGTs to modulate proteolytic turnover of nuclear nSREBPs could terminate transactivation function. Taking these findings together we propose a mechanism whereby UGTs control the balance between activation and termination of SREBP signalling. The finding that UGTs may be novel regulators of lipid biosynthesis may help explain their association with poor breast cancer outcomes and prompts their further investigation as novel biomarkers or therapeutic targets.

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Exploring the TRAIL of doxorubicin-induced cardiotoxicity

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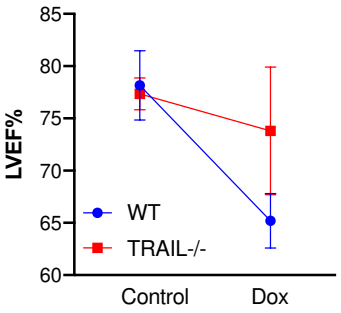
Introduction: Doxorubicin (DOX) is a widely prescribed chemotherapeutic used to treat both solid and haematologic malignancies. However, its use is limited by irreversible cardiotoxicity, which can lead to lifelong, sometimes fatal, heart complications. Recent evidence suggests the involvement of the TNF-related apoptosis-inducing ligand (TRAIL) which, through binding to its death receptors 4 and 5 initiates a signalling cascade leading to cell death. We hypothesise DOX upregulates death receptors in cardiomyocytes resulting in their sensitisation to TRAIL-induced death.

Aims: To investigate the role of TRAIL and its signalling pathway in DOX cardiotoxicity.

Method: Using cultured human cardiomyocytes, we assessed the ability of DOX to elicit cardiomyocyte death, and measured changes in death receptors using flow cytometry. Wildtype and TRAIL knockout mice (TRAIL-/-) (n=7 per group) were also used to evaluate the effect of TRAIL deficiency on cardiotoxicity following chronic DOX dosing. Cardiac function was assessed by measuring left ventricular ejection fraction (LVEF) and fractional shortening (FS) using echocardiography. T-tests and two-way ANOVAs were applied for statistical analysis where appropriate.



Results: In cell culture, we showed that (i) DOX treatment of cardiomyocytes was cytotoxic only in the presence of TRAIL; (ii) death receptor 5 on cardiomyocytes increased significantly (98%) with DOX treatment; and (iii) blockade of TRAIL signalling protected human cardiomyocytes from DOX-induced death. In wildtype mice, DOX caused a 15.6% ($p<0.0001$) and 24% ($p<0.0001$) reduction in LVEF (Figure) and FS respectively, whereas DOX treated TRAIL-/- mice had no significant reduction in cardiac function.

Discussion: Our data supports the hypothesis of DOX sensitisation of cardiomyocytes to TRAIL-induced death. Collectively, these findings strongly support TRAIL blockade as a novel therapeutic strategy to limit or eliminate DOX-induced cardiotoxicity and identify several targets for therapeutic intervention.

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The prevalence of medication-related hospital admissions in Australia: a systematic review and meta-analysis

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Introduction. Medications have an important role in the treatment of disease and improvement of health outcomes. However, despite intended benefits, medication use can also result in inadvertent harm. Medication-related problems are common and can have significant effects on morbidity and mortality, with complications ranging from mild adverse effects to significant illness and death. The prevalence of medication-related hospitalisations was previously determined to be approximately 2-3% in Australia in 2009, however more recent estimates are not available.

Aims. To investigate the prevalence of medication-related hospitalisations in Australia since 2009.

Methods. A systematic review was conducted to find literature reporting both medication-related hospitalisations and overall hospitalisations, spanning 2009-2019. Databases searched were MEDLINE, Embase, CINAHL and PubMed. Prospective and retrospective studies were included. A pooled prevalence figure and 95% CIs were calculated.

Results. Of the 1177 records screened, twelve studies met inclusion criteria and were included in the qualitative synthesis, with nine included in the meta-analysis. We found that 9% (95% CI, 5%-17%) of hospitalisations in Australia are medication-related, with the estimate varying depending on method of detection. The prevalence of medication-related admissions is 6% (95% CI, 2%-15%) based on International Classification of Diseases-10th revision-Australian Modification (ICD-10-AM) coding and 12% (95% CI, 8%-20%) based on pharmacist review. Patients taking cardiovascular drugs or aged over 65 years are most commonly associated with these admissions.

Discussion. Medication-related problems account for large numbers of Australian hospitalisations. Our pooled prevalence is greater than that reported in 2009, indicating that these problems may be increasing. This burden is likely underestimated by routine coding. Differences between ICD-10-AM coding and pharmacist review suggest that coding of medication-related problems should be standardised to avoid omission of information. Increased vigilance by healthcare providers is required to prevent, identify and manage medication-related problems, particularly for older patients and those with cardiovascular conditions.

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National suicide prevention strategies by reducing access to poisons: a systematic review

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Introduction. Suicide is a significant and preventable cause of death worldwide. Many suicide attempts are impulsive with very brief periods of risk. Means restriction (limiting public access to lethal suicide methods) aims to reduce rates of completed suicide. Firearms restrictions and bridge barriers have been shown to prevent suicide, however relatively little is known about the impact of means restriction on suicide by poisoning.

Aims. To identify the impact of national means restriction policies on suicide by poisoning.

Methods. We conducted a systematic review according to PRISMA guidelines. We searched five databases (Medline, Embase, PsycInfo, Scopus, Web of Science) for studies on means restriction of poisons published up until December 31, 2019. We included studies with country-level poisoning means restriction legislation that included data on suicide rates after the intervention.

Results. We screened 7641 articles and found 55 studies that met the inclusion criteria (and an additional 14 from other sources). The studies detailed means restriction in 26 countries. The most common interventions reported were: pesticide restrictions (16 countries) including 5 countries that banned paraquat, detoxification of domestic gas to reduce carbon monoxide exposure (14 countries) and catalytic converters to reduce carbon monoxide in motor vehicle exhaust (8 countries). Studies on pharmaceuticals included restriction of barbiturates (4 countries), withdrawal of dextropropoxyphene/propoxyphene (5 countries) and pack-size limits of paracetamol and salicylate tablets (2 countries). 66 studies reported a decline in method-specific suicide rates following the intervention. Of these, method substitution (overall suicide rates unchanged/increasing) was reported in 16.

Discussion. Most studies reported a decrease in suicide rates by the specific method of interest, while the response of overall suicide rates in the population varied. Means restriction of poisons is overall an effective suicide prevention strategy, but can be difficult to compare due to populations being dynamic and varied. Ideally, a combination of suicide prevention strategies can be implemented, with continuous monitoring of suicide rates and a fast response to any rapidly rising trends.

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Harm from cardiovascular medications: the omitted 'C'

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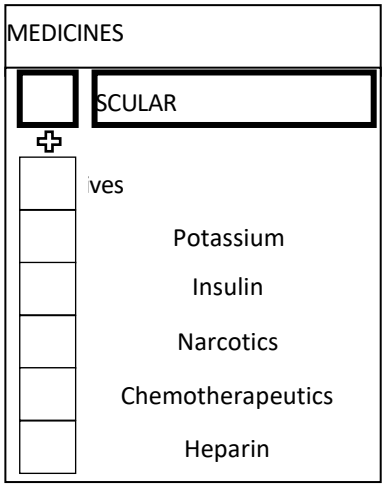

Introduction. Medication harm can lead to hospital admission, prolonged hospital stay and poor patient outcomes. Reducing medication harm is the World Health Organisation's third patient safety challenge. Cardiovascular (CV) medications have the potential to cause significant medication harm. However, they appear to receive less recognition as *'high-risk'* medications compared to those classified by the medication safety acronym, '*APINCH*' (see Figure).

Aim. To determine the scale and burden of medication harm caused by CV medications in healthcare.

Methods. A narrative review of medication harm literature identified from PubMed and CINAHL databases since 1990 was undertaken. Studies with the primary outcome of measuring the incidence of medication harm were included. Harm caused by CV medications was described and ranked against other medication classes at four key stages of the healthcare journey: hospital admission, during hospital stay, post discharge and readmission. The implicated medications and type of harm were investigated.

Results. A total of 75 studies were identified, including seven systematic reviews and three meta-analyses with most focussing on harm causing hospital admission. CV medications were responsible for approximately 20% of medication harm in each healthcare setting, however, this proportion increased to 50% in older populations. CV medications were consistently ranked in the top five medication categories causing harm and were often listed as the leading cause.

Discussion. CV medications are a leading cause of medication harm, particularly in older adults, and should be the focus of harm mitigation strategies. A practical approach to generate awareness is to incorporate *'C'* (for CV medications) into the *'APINCHS'* acronym. *'CAPINCH'* (see Figure) would serve as a prompt to optimise the use of CV medications.

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The prevalence and characteristics of psychotropic-related hospitalisations in older people: a systematic review and meta-analysis

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Introduction. Psychotropic medications are increasingly prescribed to older people to manage a range of mental health conditions. However, older people are more prone to the adverse effects of these medications. Psychotropic medications may thus carry a high risk of unplanned hospitalisations in this population.

Aims. To assess the prevalence and characteristics of psychotropic medication-related hospitalisations in older people.

Methods. A systematic review and meta-analysis was conducted. Databases searched included: Medline, Embase, CINAHL and Scopus from 2010 to March 2020. A meta-analysis was conducted to estimate pooled prevalence and 95% confidence intervals (CIs) of psychotropic-related hospitalisations using random effects models. Heterogeneity was further explored using subgroup analyses.

Results. Of 815 potentially relevant studies, 11 were included in the final analysis. The majority of studies were rated as good quality (n=10). Most studies used International Classification of Diseases (ICD) coding (n=5) or independent assessment (n=5) to identify adverse drug events (ADEs). Psychotropic medications contributed to 2.1% (95% CI, 1.2-3.3%) of total hospitalisations and 11.3% (95% CI, 8.2-14.8%) of ADE-related hospitalisations. The main psychotropic medications attributable to hospitalisations were hypnotics, sedatives and antidepressants. Primary clinical presentations included falls, delirium and hyponatremia. Women and those with polypharmacy and multimorbidity were found to be at greatest risk of hospitalisation.

Discussion. Psychotropic medications are a significant contributor to hospitalisations in older adults. Future studies should aim to address specific medication subgroups, strategies to optimise medication management in older people, and implement uniform ADE classification systems to improve comparability across studies.

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Characterising G protein coupling of angiotensin II and bradykinin receptor heteromers using mini G proteins

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Introduction. The renin-angiotensin system and the kallikrein-kinin system constitute two regulatory systems involved in the maintenance of blood pressure. Interactions between the two systems are numerous and have been extensively studied for decades. The establishment of the concept of G protein-coupled receptor (GPCR) heteromerisation has now revealed new potential interactions between the two systems, including heteromers between the angiotensin type 1 (AT_1) and type 2 (AT_2) receptors and the bradykinin type 2 (B_2) receptor. These receptors form three heteromers whose pharmacology has been investigated to varying extents. We have utilised the recently developed mini G protein biosensors (Wan et al., 2018) to characterise each of the heteromer's G protein coupling profiles.

Aims. To investigate the G protein coupling pharmacology of the AT_1-AT_2 heteromer, the AT_1-B_2 heteromer and the AT_2-B_2 heteromer.

Methods. Bioluminescence resonance energy transfer (BRET) labelled receptors and mini G proteins were coexpressed in HEK293FT cells. Assays with only one receptor expressed enabled profiling of individual receptor pharmacology, while coexpression with an unlabelled receptor allowed potential heteromer pharmacology to be identified using the GPCR-heteromer identification technology (GPCR-HIT) configuration (See et al., 2011).

Results. The individual receptors displayed G protein coupling preferences as expected for those receptors. Some novel G protein pharmacology was observed in the heteromer assays, such as ligand-induced G protein recruitment proximal to the AT_2 receptor, which does not normally couple to G proteins.

Discussion. This study has demonstrated the application of the mini G protein biosensors for investigating GPCR heteromers, and has also revealed some novel G protein pharmacology attained upon heteromerisation.

See et al. (2011) Assay & Drug Devel Tech 9(1):21-30.
Wan et al. (2018) J Biol Chem 293:7466-7473

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A new pertussis toxin-like protein complex as a tool for investigation of GPCR-$G\alpha_i$ and $G\alpha_z$ signalling

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Introduction. AB_5 toxins such as pertussis toxin are heterohexameric protein complexes secreted by pathogenic bacterial species. The B subunits of AB_5 toxins bind host cell surface receptors and provide entry to the cells. The catalytically active A subunit then acts on intracellular proteins to modify cell signalling and cell behaviour. Due to their actions, AB_5-type toxins have become useful tools for delineating intracellular signalling pathways and understanding cellular processes. Recently, a novel pertussis toxin-like family AB_5 toxin was identified and characterised (Littler et al, 2017). The toxin was reported to act similarly to pertussis toxin by ADP-ribosylating heterotrimeric G proteins preventing their interaction with and activation by G protein coupled receptors. It was, however, shown to act at a structurally distinct amino acid site on the G protein.

Aims. We aimed to characterise the substrate specificity of the new pertussis toxin-like protein and further validate it as a tool for GPCR-G protein signalling studies.

Methods. Activation of individual Gα subunits by GPCRs was assessed using bioluminescence resonance energy transfer (BRET) G protein activation assays via transient transfection in Gα-all CRISPR knockout HEK293 cells. Intracellular cAMP BRET assays were performed in $G\alpha_{i/o}$ CRISPR knockout HEK293 cells.

Results. Overnight treatment with the toxin abolished the GPCR mediated activation of all tested $G\alpha_{i/o}$ subfamily G proteins including the pertussis toxin insensitive - $G\alpha_z$. The toxin did not inhibit activation any other heterotrimeric G protein family member. Transfection of cDNA encoding the active A subunit was sufficient to inhibit G protein activation. Furthermore, $G\alpha_{i/o}$ subfamily G proteins could be made insensitive to the toxin through mutagenesis.

Discussion. This new toxin may be used as a tool in combination with pertussis toxin for understanding the function of inhibitory family heterotrimeric G proteins including $G\alpha_z$. This study warrants further investigations into unexplored AB_5 toxins in an effort to find more molecular tools.

References. Littler et al (2017) J Biol Chem 292: 15143-15158

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Differential G protein activation kinetics may underpin the beneficial aspects of clinically trialled A_1R atypical agonists

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Introduction. Activation of adenosine A_1 receptors (A_1Rs) represents a powerful strategy for the treatment of cardiovascular disease. Clinically trialled atypical A_1R agonists, capadenoson and neladenoson, stimulate cardioprotection (Sabah et al, 2013) with minimal bradycardia (Shah et al, 2019; Sabah et al, 2013), a signalling profile typically attributed to reduced intrinsic efficacy. However, capadenoson and neladenoson are biased A_1R agonists (Baltos et al, 2016; Rueda et al, 2020), and as such a better mechanistic understanding is required to facilitate the rational design of more effective A_1R therapeutic candidates. Aim. To quantify A_1R-mediated Gβγ-effector interactions in response to prototypical and atypical A_1R agonists; as Gβγ-GIRK channel interactions are the direct mechanism for A_1R-mediated bradycardia. Methods. Stably expressing A_1R-HEK293A cells with all G proteins deleted were transiently transfected with masGRKct-nanoluc, $G\alpha_{oA}$, and $G\beta_1\gamma_2$-venus. The masGRKct construct readily binds free Gβγ dimers, on a timescale that mirrors GIRK channel activation (Hollins et al, 2009). Results. The prototypical agonist MeCCPA and capadenoson were equipotent with a similar maximal response (pEC_{50}: 6.6 – 6.9; n=3-4, P>0.05). However, the onset kinetics of $G\beta_1\gamma_2$ interactions atypical agonists were significantly reduced by 4-8 fold as compared to prototypical agonists (n=3-4, P<0.05). Discussion. Considering the similar potency and maximal response observed for MeCCPA and capadenoson, the different kinetic profile of Gβγ-effector interactions may have a key role in conferring the clinically beneficial profile of atypical A_1R agonists.

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Hollins B et al (2009) Cell Signal 21(6):1015-1021
Rueda P et al (2020) bioRxiv preprint doi: https://doi.org/10.1101/2020.07.22.215509
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The structural basis for the UDP-sugar selectivity of human UDP-glycosyltransferase 2B7 (UGT2B7): A combined computational and experimental approach.

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Introduction. Enzymes of the human uridine diphosphate (UDP)-glycosyltransferase (UGT) superfamily catalyse the covalent addition of the sugar moiety from a UDP-sugar cofactor to relatively low molecular weight lipophilic substrates. UGT2B7 can utilise both UDP-glucuronic acid (UDP-GlcUA) and UDP-glucose (UDP-Glc) as cofactors. However, glucuronidation is the preferred metabolic pathway. Currently, it is unclear which residues in the UGT2B7 cofactor binding domain are responsible for the preferential binding of UDP-GlcUA.

Aims. I) Identify key residue(s) associated with the selective binding of UDP-GlcUA over UDP-Glc using molecular dynamics simulations (MDS). 2) Experimentally validate the observations from MDS using site-directed mutagenesis (SDM) and enzyme activity assays.

Methods. Molecular dynamics simulations were performed with a UGT2B7 homology model. UDP-GlcUA and UDP-Glc were docked in the cofactor binding site of the protein. The Arg259Leu mutant was generated by SDM. Enzyme kinetic studies were performed on wild-type UGT2B7 and the Arg259Leu mutant using zidovudine, morphine and 4-methylumbelliferone as the substrate probes.

Results. MDS demonstrated that multiple residues in the C-terminal domain of UGT2B7 stabilise the binding of both UDP-GlcUA and UDP-Glc. However, Arg259 in the N-terminal domain additionally forms a salt-bridge and H-bonds with UDP-GlcUA, whereas no interactions were noted between Arg259 and UDP-Glc. Wild-type UGT2B7 glucuronidated all three probe substrates, but the Arg259Leu mutant lacked glucuronidation activity. By contrast, morphine 3-glucosidation formation was unaffected by the Arg259 to Leu substitution.

Discussion. Although both UDP-GlcUA and UDP-Glc can bind in the active site of UGT2B7, binding of the former is favoured by interactions between Arg259 and the carboxylate group of UDP-GlcUA. The conformational 'locking' of UDP-GlcUA within the active site results in a higher binding affinity compared to UDP-Glc, which lacks a carboxylate group. Since Arg259 is conserved in drug metabolising UGT enzymes, glucuronidation is predicted to be the major metabolic pathway.

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Characterisation of the G protein coupling profiles of PAC1 receptor splice isoforms

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Introduction. The pituitary adenylate cyclase-activating polypeptide (PACAP) type I receptor (PAC1R) is an attractive therapeutic target for the treatment of many CNS diseases including migraines and post-traumatic stress disorder (Rubio-Beltrán et al, 2018; Ressler et al, 2011). Extensive alternative splice isoforms of PAC1R have been identified. These isoforms contain alterations in the intracellular loop 3 (ICL3) and/or the N-terminal extracellular domain (ECD). Previous studies have suggested distinct signalling properties of these isoforms (Lutz et al, 2006). However, comprehensive characterisation of their transducer coupling, activation and regulation profiles is currently lacking.

Aim. In this study, we have characterised the G protein coupling profiles of PAC1R isoforms, including the most common splice isoform, termed PAC1 null (PAC1n) and variants with a truncated ECD (PAC1s), in addition to variants that contain ICL3 insertions (hip, hop or hiphop) using TRUPATH G protein biosensors.

Methods. PAC1R isoforms and TRUPATH biosensors were transiently transfected into COS-7 cells and treated with increasing concentrations of agonists: PACAP-38, PACAP-27, vasoactive intestinal peptide (VIP) and maxadilan. Real-time G protein dissociation profiles of G_{s}, G_{i}, $G_{q/11}$ and G_{12} were measured at 37°C using PHERAstar (BMG Biotech).

Results. Insertions in ICL3 altered the G-protein coupling profiles of PAC1n and PAC1s. PAC1n-hop displayed a four-fold increase in PACAP-38 potency for $G_{q/11}$ coupling (G_{q} pEC_{50}: 8.4±0.1; G_{11} pEC_{50}: 8.3±0.1) compared to PAC1n (G_{q} pEC_{50}: 7.8±0.2; G_{11} pEC_{50}: 7.8±0.2). While, insertions of the hip and hiphop cassettes led to weaker G_{i1} coupling. PAC1s increased the potency of VIP-mediated G protein coupling for all four G protein subtypes.

Discussion. Altered G protein coupling profiles of the PAC1R ICL3 variants contribute to their overall signalling profile, while splice isoforms in the N-terminal ECD reduced functional coupling to all G proteins and may be indicative of reduced ligand affinity. The results from this study provide insight into the signalling mechanisms of PAC1R.

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Ressler KJ et al (2011) Nature 470:492-497
Rubio-Beltrán E et al (2018) J Headache Pain 19:64

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The use of AI to enhance the success and efficiency of drug discovery and development

Jackie Hunter, BenevolentAI, UK

BenevolentAI is building technology that augments human intelligence in order to empower scientists to uncover vital new therapeutics for patients. In this presentation, Jackie Hunter will discuss how BenevolentAI's unique biomedical knowledge graph and computational tools allow scientists to predict more accurately which paths are most likely to lead to effective therapies by enhancing chemical drug design and precision medicine. Case studies, including BenevolentAI's successful research into a potential treatment for COVID-19, and challenges in implementation will also be discussed.

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Plant with the scorpion sting: pharmacology of Australia's most venomous plant "Gympie-Gympie"

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Introduction. Australia notoriously harbors some of the world's most venomous animals, but less well-known are its equally remarkable venomous flora. Australian stinging nettles from the genus *Dendrocnide* are renowned for producing excruciatingly painful and persistent stings caused by contact with their needle-shaped hairs.

Aims. The aim of this study was to investigate the pharmacological basis of pain induced by the giant Australian stinging tree "Gympie-Gympie".

Methods. Activity-guided fractionation of *D. excelsa* venom identified a single pain-causing fraction containing a family of disulfide-rich peptides containing 36 amino acid residues. One of these peptides, named ExTxA, was chemically synthesized and pharmacological activity was assessed using single fibre recordings, calcium imaging and patch-clamp electrophysiology on sensory neurons.

Results. Application of ExTxA (100 nM) to the receptive fields of mechanosensitive A- and C-fibers caused spontaneous action potential (AP) firing, confirming direct activation of primary sensory neurons. ExTxA (10 nM) caused Ca^{2+} influx in the majority of neurons (68%) that was significantly reduced (26%) by tetrodotoxin (TTX; 1 µM), suggesting activity at voltage-gated sodium channels (Na_V). Indeed, ExTxA potently and irreversibly delayed fast inactivation of voltage-gated sodium channels (EC_{50} 58 nM), providing a pharmacological basis for sting-induced pain.

Discussion. Pharmacological activity of ExTxA is particularly remarkable given that the primary structure is unique, with only very limited similarity to known sequences, while the function of ExTxA is reminiscent of α-scorpion toxins. This makes ExTxA the first plant-derived knottin with activity at Na_V channels reported to date, forming a novel class of plant peptides exemplifying convergent evolution of neurotoxins

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An adaptive e-tutorial for development of critical appraisal skills

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Introduction: Critical thinking is a Threshold Learning Outcome for biomedical science students. 'Research Inquiry', a core unit in 2 Masters degrees, aims to equip students with critical appraisal skills. Common to many postgraduate degrees, our students have a variety of academic backgrounds. In the final exam, designed to assess ability to critically appraise a neuropharmacology paper, there is disparity in performance according to academic background.

Aims: To improve critical appraisal abilities across the whole cohort, regardless of academic background.

Methods: We developed an adaptive e-tutorial using Smart Sparrow, allowing personalised feedback and remediation. It included key appraisal concept revision, a neuropharmacology-based scenario for appraisal practice, and 8 self-developed animated videos for remediation. Effectiveness was measured with an end-of-tutorial survey, and by comparing the Unit of Study Survey ratings and exam results in the 2 years before, and during the intervention.

Results: 150 students participated over 4 years. In the cohorts that did not complete the e-tutorial, there were significant differences in exam marks between all groups (non-science<science<medicine backgrounds), while no significant differences between groups were seen in students that completed the e-tutorial (one-way ANOVA with Sidak's post-hoc test; $p<0.05$), and these marks were statistically equivalent (independent groups Welch's Equivalence Test, $p<0.05$, equivalence bounds=20). Students ranked their perceived benefit from the videos, increase in critical appraisal ability, and value of the e-tutorial with average rankings between 4.4-4.6 on a Likert scale (where 5=strongly agree). Similarly, students who completed the e-tutorial showed a significant increase in rating of their critical thinking skills in the Unit of Study Survey ($p<0.05$). A YouTube traffic source analysis showed that over 50 universities have embedded some of the remediation videos on their university e-learning platforms.

Discussion: Completion of the e-tutorial was associated with increased equitable development of critical appraisal. Students from non-science backgrounds showed the biggest increase in actual appraisal performance, suggesting that while the e-tutorial increased confidence for all students, the other features of the course may have developed appraisal levels to a stage sufficient for successful exam completion.

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Global solutions to global challenges-prioritising our efforts

Prof Parisa Aslani, The University of Sydney, NSW, Australia

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Biased negative allosteric modulators for the calcium-sensing receptor have differential bronchodilator and bronchoprotective effects in mouse precision cut lung slices

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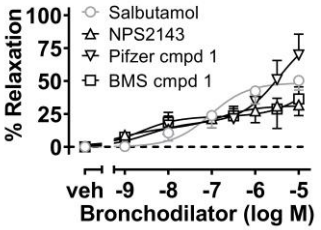

Introduction. The calcium-sensing receptor (CaSR) detects changes in extracellular calcium (Ca^{2+}_o) to maintain Ca^{2+}_o homeostasis. The CaSR is upregulated in asthma, and CaSR negative allosteric modulators (NAMs) reduce inflammation, remodelling, and airway hyperresponsiveness in a mouse model of chronic allergic airways disease (Yarova et al, 2015). Whether CaSR NAMs, which engender biased modulation (Davey et al, 2012), have different bronchodilator and/or bronchoprotective effects is unknown.

Aim. To assess CaSR NAM (NPS2143, Pfizer cmpd 1, BMS cmpd 1) bias in CaSR-HEK293 cells and compare NAMs with the β_2-adrenoceptor agonist salbutamol for airway relaxation.

Methods. Intracellular calcium (Ca^{2+}_i) mobilisation and IP_1 accumulation assays in CaSR-HEK293 cells were used to quantify the affinity and cooperativity of CaSR NAMs. Precision cut lung slices from male C57Bl/6 mice were prepared to visualise changes in airway area after contraction stimulated by 300 nM methacholine (MCh) followed by NAM or salbutamol (bronchodilation assays) or after overnight pre-incubation with 1 µM NAMs (bronchoprotection assays).

Results. CaSR NAMs engendered differential and biased modulation of Ca^{2+}_i mobilisation and IP_1 accumulation. CaSR NAMs relaxed pre-contracted airways in a biphasic manner (see figure), with the highest potency first phase of their response being 1000-fold higher potency than salbutamol. Salbutamol and NAMs caused comparable maximal bronchodilation (salbutamol 50±7%, NPS2143 32±8%, Pfizer cmpd 1 70±16%, BMS cmpd 1 48±16%, n=4-6). Overnight incubation with NPS2143 and Pfizer cmpd 1, but not BMS cmpd 1 prevented contraction.

Discussion. CaSR NAMs show differential effects on MCh-induced airway contraction, with Pfizer cmpd 1 exhibiting greater bronchodilator efficacy and potency than salbutamol. Confirmation of benefit compared to salbutamol in asthmatic airways would further support the CaSR as a novel therapeutic target for the treatment of asthma.

Yarova et al (2015) Sci Transl Med. 7:284
Davey et al (2012) Endocrinology. 153:1232

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Effects of ABC transporter modulation on olanzapine entry into the developing brain

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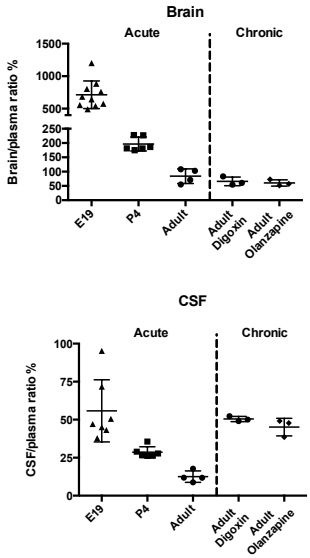

Introduction. Many women with psychiatric disorders at childbearing age would have to continue medicating throughout pregnancy and lactation as cessation is potentially dangerous for both mother and child. However, information on antipsychotic drug transfer into the developing brain is limited.

Aims. i) To measure the transfer of olanzapine across placental and blood-brain barriers in rats during development following acute (single dose) or chronic (multiple doses) treatment with the drug. ii) To determine age-related effects of co-administering a known ABC transporter modulator, digoxin (Koehn et al., 2019) on olanzapine permeability.

Methods. Sprague Dawley rats were injected i.p. with 0.15mg/kg of olanzapine containing a radioactive olanzapine tracer at 3 ages (E19, P4, adult). In acute experiments, a single olanzapine dose was injected 30min before sample collection. In chronic experiments, either digoxin (30ug/kg) or olanzapine (0.15mg/kg) were given daily for 5 days. Transfer of olanzapine in the blood, brain and CSF was measured using liquid scintillation counting.

Results. An age dependent decrease in transfer into brain (from 848%±213 at E19, to 84%±26 in adult) and CSF (from 89%±21 at E19 to 13%±4 in adult) was observed after exposure to olanzapine (see Figure above). In pregnancy, around 20% of the drug was transferred from the maternal blood to the fetal circulation. In chronic experiments in adults, brain transfer of the drug remained at a similar level to acute treatment (around 60%). However, transfer of olanzapine into the CSF, compared to acute exposure (13%±4, n=4), significantly increased after both repeated olanzapine (45%±6, n=3) or digoxin treatments (51%±2, n=3) as illustrated in the Figure above.

Discussion. The developing brain has lower ability to restrict drug entry, resulting in their increased levels. Use of ABC transporter modulators in conjunction with antipsychotic substrate drugs may not limit drug transfer into the brain or CSF at clinical doses.

Koehn et al (2019) F1000Res 8;1372

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Evaluation of a combination therapy that provides broad renoprotection against DOCA/salt-induced hypertension

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Introduction. Fibrosis is a hallmark of chronic kidney disease (CKD) and can impair the efficacy of stem cell-based therapies. We found that combining human bone marrow-derived mesenchymal stem cells (BM-MSCs) with the anti-fibrotic drug, serelaxin (RLX), effectively prevented the progression of renal fibrosis to a greater extent than either therapy alone, in a normotensive model of tubulointerstitial renal disease. As hypertension is a leading risk factor for CKD, we determined the therapeutic effects of this combination therapy in a model of hypertensive kidney disease.

Aim. To compare the anti-fibrotic and renoprotective effects of BM-MSCs, RLX, and their combined effects to a clinically-used angiotensin converting enzyme inhibitor (ACEi), perindopril, in a murine model of one kidney/deoxycorticosterone acetate/salt (1K/DOCA/salt)-induced hypertension.

Methods. 10-12 week-old male C57BL/6 mice were uninephrectomised, received subcutaneous (s.c) implantation of a DOCA pellet (2.4 mg/day) and were maintained on 0.9% saline (1K/DOCA/Salt) for 21 days. Control mice were uninephrectomised and received normal drinking water over the same time-period. From days 14-21, sub-groups of 1K/DOCA/salt mice (n=5-8 mice/group) were either left untreated, or treated with RLX (0.5mg/kg/day via 7-day s.c osmotic minipumps), BM-MSCs ($1x10^6$/mouse; single intravenous (i.v) injection on day 14), both treatments combined (with $0.5x10^6$ or $1x10^6$ BM-MSCs/mouse, i.v + 0.5mg/kg/day RLX, s.c) or perindopril (2mg/kg/day via drinking water).

Results. 1K/DOCA/salt-injured mice developed elevated blood pressure (BP) and hypertension-induced renal structural damage, inflammation and fibrosis. By 7 days post-treatment, BM-MSCs alone attenuated BP to a similar extent as perindopril and ameliorated the 1K/DOCA/salt injury-induced interstitial fibrosis and total collagen concentration. RLX alone modestly reduced fibrosis and effectively attenuated tubular epithelial injury. Strikingly, the combined effects of BM-MSCs and RLX exhibited equivalent anti-hypertensive effects as perindopril, and offered more broader anti-fibrotic efficacy and renoprotection compared to either therapy alone or the effects of perindopril.

Discussion. Combining BM-MSCs and RLX, which incorporates the BP-lowering effects of BM-MSCs and the individual and overlapping renoprotective effects of BM-MSCs or RLX, might represent a novel treatment for hypertensive CKD.

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Cigarette smoking does not worsen skeletal muscle contractile function or loss caused by acute viral infection in mice

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Introduction. Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation that is largely attributed to cigarette smoking (CS). Skeletal muscle wasting is a prevalent comorbidity that affects up to 40% of COPD patients. Muscle wasting is most frequently reported following an episode of viral-induced acute exacerbation of COPD (AECOPD), which may prolong hospital stay and lead to future readmission. However, the underlying mechanisms responsible remain poorly defined.

Aims. To investigate whether viral infection per se causes muscle wasting and dysfunction *in vivo*, and if so, determine whether such an effect would be amplified by chronic CS exposure.

Methods. Male BALB/c mice were exposed to either room air (sham) or CS (9 cigarettes per day, 5 days per week) for 8 weeks followed by inoculation with either influenza A virus (IAV; Mem71, $1x10^{4.5}$ PFU) or diluent (PBS) and culled 3 days post-infection. Muscle function tests were performed, and prime mover muscles of the hind limbs were collected for morphological analyses.

Results. IAV infection resulted in no change in tibialis anterior (TA) muscle mass, despite marked lung inflammation evidenced by a 11.6-fold increase in bronchoalveolar lavage fluid cellularity (p<0.001 vs sham diluent, n=10). CS exposure alone induced a 13% loss in TA muscle mass (p<0.001 vs sham diluent; n=10). When CS exposure was combined with IAV infection, lung inflammation was exacerbated 2-fold (p<0.001 vs CS diluent), however, no further reduction in TA muscle mass was observed (p=0.99 vs CS diluent). Despite the unchanged muscle mass, the strength of TA was reduced by 52% by IAV infection (p<0.001 vs sham diluent, n=6) which was not further compromised by CS exposure (p=0.20 vs sham IAV, n=6).

Discussion. Acute IAV infection per se specifically impaired muscle function without muscle loss. This suggests that muscle function may be more vulnerable to IAV infection than muscle mass. The lack of an additive effect may imply the involvement of mechanisms other than simple lung inflammation in driving the observed muscle dysfunction.

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Deletion of orphan GPCR, GPR37L1, alters autonomic control of cardiovascular homeostasis in mice

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Introduction. GPR37L1 is an orphan G protein-coupled receptor with a reported role in maintaining blood pressure (Min et al, 2010), though a mechanistic explanation for this is currently unclear. Since GPR37L1 is expressed highly in the brain and not in the heart or kidney (Coleman et al, 2018), we propose GPR37L1 may alter autonomic control of the cardiovascular system.

Aims. This series of experiments was designed to identify whether GPR37L1 is necessary for normal autonomic system control of cardiovascular homeostasis.

Methods. Blood pressure, heart rate (HR) and locomotor activity were recorded by radiotelemetry in C57BL/6J and GPR37L1$^{-/-}$ mice of both sexes. Auto- and cross-spectral power analysis of mean arterial pressure (MAP) and HR was used to decipher cardiovascular autonomic contribution. Pharmacological ganglionic blockade (pentolinium) was used to determine sympathetic vasomotor tone. Cardiovascular reactivity to stress was determined by subjecting mice to acute physical stress tests (dirty cage swap, restraint, palatable food presentation) while telemetered.

Results. GPR37L1$^{-/-}$ genotype had a statistically significant positive effect on HR across both sexes (genotype effect p=0.0002, two-way ANOVA). Both sexes of GPR37L1$^{-/-}$ mice exhibited attenuated depressor responses to ganglionic blockade, indicating reduced sympathetic vasomotor tone. There was a reduction in the night-time HR power spectra of female GPR37L1$^{-/-}$ mice within a frequency band correlated with vagal drive. Interestingly, female GPR37L1$^{-/-}$ mice exhibited an attenuation of cardiovascular reactivity to aversive, but not appetitive, environmental stimuli.

Discussion. Together, these results suggest that loss of GPR37L1 impairs vagal drive of HR, reduces sympathetic vasomotor tone, and differentially affects male and female cardiovascular responses to stress.

Min et al. (2010) Biochem Bioph Res Co 393:55-60
Coleman et al. (2018) Biol Sex Differ 9:14

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The nitroxyl donor Angeli's salt circumvents nitric oxide resistance in the insulin-resistant diabetic myocardium

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Introduction. Diabetes increases mortality risk due to cardiovascular complications, which are partially driven by impairments in nitric oxide (NO•) signalling at the level of tissue responsiveness, known as NO• resistance.

Aims. To investigate whether diabetes promotes, and nitroxyl (HNO) circumvents, NO• resistance in the myocardium.

Methods. At 8 weeks of age, male Sprague-Dawley rats were fed a high-fat diet and 2 weeks later received low-dose streptozotocin (2x35 mg/kg ip, over 2 consecutive days). At 22 weeks of age, we assessed responses to the NO• donor diethylamine NONOate (DEA/NO) and the HNO donor Angeli's salt in Langendorff-perfused hearts. Responses to insulin were also examined in Langendorff-perfused hearts to assess cardiac insulin sensitivity. Data are expressed as change from baseline (Δ) and were analysed by Student's unpaired t-test. *P<0.05 vs non-diabetic (ND) hearts.

	DEA/NO (10^{-5} M)		Angeli's salt (10^{-5} M)		Insulin (33.3 IU)	
	ND (n=8)	Diabetic (n=8)	**ND** (n=8)	Diabetic (n=9)	**ND** (n=7)	Diabetic (n=9)
ΔLVDP (mmHg)	5.7±0.7	2.3±0.6*	4.1±0.7	10.2±1.4*	20.3±2.7	6.3±1.9*
ΔLVEDP (mmHg)	2.6±0.6	1.1±0.2*	1.8±0.3	1.6±0.2	1.5±0.2	0.8±0.2*
ΔLV+dP/dt (mmHg/s)	147±19	96±18*	121±11	183±19*	371±45	83±17*
ΔLV-dP/dt (mmHg/s)	-133±8	-78±7*	-102±13	-153±14*	-339±46	-82±15*
ΔCoronary flow (mL/min)	7.0±0.7	4.6±0.9*	6.5±0.7	7.7±1.1	1.8±0.3	1.0±0.1*
ΔHeart rate (bpm)	14.5±2.3	21.2±1.3*	9.6±1.0	11.8±1.2	4.8±0.8	4.0±1.0

Results. Myocardial insulin resistance was evident in diabetic hearts, as demonstrated by blunted inotropic, lusitropic and coronary vasodilator responses to insulin. In response to DEA/NO, inotropic, lusitropic and coronary vasodilator responses were impaired in diabetic hearts, whereas responses to Angeli's salt were enhanced or preserved.

Discussion. These findings demonstrate for the first time that the HNO donor Angeli's salt circumvents NO• resistance in the diabetic insulin-resistant myocardium, highlighting the therapeutic potential of HNO donors to treat acute diabetes-associated impairments in cardiac function.

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Predictive performance of population pharmacokinetic models for tacrolimus in lung transplant recipients

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Introduction. Bayesian forecasting software may assist in optimising therapeutic drug monitoring for tacrolimus. However, the most appropriate population pharmacokinetic (popPK) model to be utilised in software to predict tacrolimus exposure in lung transplant (LTX) recipients remains unclear.

Aims. To evaluate and compare the predictive performance of popPK models in post-operative LTX patients. To identify factors which influence the predictive performance.

Methods. Retrospective data from adult LTX patients administered tacrolimus were used to evaluate the performance of 17 published popPK models to predict serum tacrolimus concentrations *a priori* (no observed concentrations included) or with Bayesian forecasting (using concentration data). Predictive performance was determined using relative bias (rBias, bias) and relative root mean squared error (rRMSE, precision). Models were considered clinically acceptable if rBias was between -20% and 20%, and the 95% confidence intervals included zero. The influence of gender, weight, cystic fibrosis (CF), azole therapy and diabetes mellitus status on model performance was assessed with multiple linear regression.

Results. Data from 41 patients (35 non-CF, 6 CF; 1514 concentrations) were used to evaluate 17 tacrolimus popPK models. No models had a satisfactory *a priori* rBias (-111.9 - -46.36). Only the model by Monchaud et al. was clinically acceptable with Bayesian forecasting (rBias -1.82%, CI -3.95 – 0.29; rRMSE 8.85%). Azole therapy was the only covariate with significant influence on the rBias and rRMSE of this model. The incorporation of azole therapy appeared to improve the accuracy of Bayesian forecasting with this model by 8.9% ($p < 0.01$).

Discussion. The model by Monchaud et al. developed exclusively from LTX recipients is suitable to guide tacrolimus dosing in LTX patients. However, a least one tacrolimus concentration is required to ensure accurate predictions.

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Intracellular enzymatic activation of 4-hydroxycylophosphamide in leukocytes.

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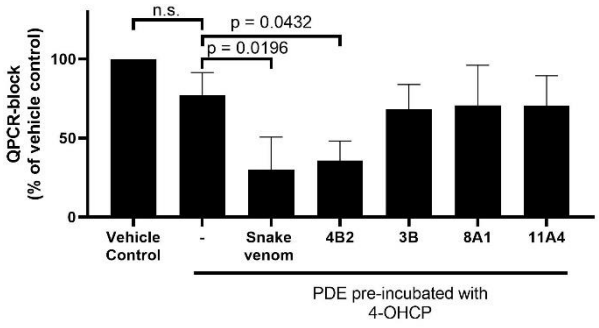
Introduction. The immunomodulatory effect of the prodrug cyclophosphamide is mediated by the metabolite phosphoramide mustard (PAM). This alkylates DNA and results in apoptosis of auto-reactive lymphocytes. Following hepatic metabolism cyclophosphamide forms 4-hydroxycyclophosphamide (4-OHCP), the precursor of PAM. 4-OHCP is thought to enter cells and then chemically degrade into PAM. However, hydrolysis of 4-OHCP can be catalysed by phosphodiesterases (PDE) from snake venom and some data suggest that this also occurs in leukocytes.

Aims. To verify that human leukocytes bioactivate 4-OHCP into the DNA alkylating agent (PAM) and to identify a role for human PDE.

Methods. Purified DNA or peripheral blood mononuclear cells (PBMC) were incubated with 4-OHCP or PAM. The amount of DNA alkylation in the template DNA was quantified by QPCR-block assay. Data from replicate experiments were plotted as IC_{50} curves. A low IC_{50} indicates high DNA alkylation. Incubation with snake venom PDE and purified human PDE isoforms were used to determine if these enzymes activate 4-OHCP.



Results. 4-OHCP was a weak alkylator of purified DNA compared to PAM (IC_{50} >1000 µg/mL vs 0.554 µg/mL). In contrast, in PMBC 4-OHCP alkylated DNA to a greater extent than PAM (IC_{50} 61.5 µg/mL vs 186 µg/mL). Snake venom PDE and human recombinant PDE4B2 activated 4-OHCP into an alkylating agent (47% and 41% increase respectively, $P<0.05$).

Discussion. This data indicates that leukocytes and PDE can activate 4-OHCP into the DNA reactive product important for its mechanism of action in autoimmune disease.

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The Influence of Haemostatic System Maturation on the Dose-Response Relationship of Unfractionated Heparin

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Introduction. Unfractionated heparin (UFH) dosing and monitoring guidelines for children are often extrapolated from adult data. This practice is considered to be suboptimal given the inherent differences in haemostatic maturation and drug handling in children compared to adults.

Aims. To investigate the impact of haemostatic system maturation on the dose-response relationship of UFH.

Methods. A quantitative model for haemostasis in adults[1] was adapted to account for maturation in UFH pharmacokinetic (PK) parameters with and without age-related changes in coagulation factor concentrations. The adult and adapted models were used to predict the time courses of anti-factor Xa activity (aXa) and activated partial thromboplastin time (aPTT) in paediatric patients receiving UFH infusion. Predictions from both models were compared to observed aXa and aPTT measurements from 31 paediatric patients receiving UFH during extracorporeal membrane oxygenation (ECMO).

Results. The model with maturation for both UFH PK and the haemostatic system had an improved performance compared to maturation in UFH PK only and the original adult model. In addition, some patients exhibited time-varying sensitivity of aPTT response. Maturation of the haemostatic system appears to correlate with maturation of the glomerular filtration process.

Discussion. We have adapted a quantitative system pharmacology model (QSP) model to provide a mechanistic and quantitative basis for linking physiological and pharmacological maturation to UFH effect and response biomarkers. Despite having similar baseline aPTT values, it appears that children can be up to twice as sensitive to UFH as adults. Anti-Xa activity is much less affected by the haemostatic maturation process. In some children, clotting factor concentrations may vary overtime producing significant within patient variability in response to treatment, which will require more intensive monitoring.

[1] Wajima et al (2009) A comprehensive model for the humoral coagulation network in humans. *Clin Pharmacol Ther*; 86(3):290-298

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Towards precision dosing of vancomycin in critically ill patients: evaluating predictive performance of pharmacometric models in Intensive Care Unit patients

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Introduction. Vancomycin dose recommendations depend on population pharmacokinetic (popPK) models. These models have not been adequately assessed in critically ill patients, who exhibit large pharmacokinetic variability (Broeker et al, 2019; Rybak et al, 2020).

Aims. (1) To identify vancomycin popPK models with clinically acceptable predictive performance specifically in Intensive Care Unit (ICU) adult patients; (2) To identify the influence of clinical parameters on predictive performance.

Methods. ICU adult patients administered vancomycin were used to evaluate model performance to predict vancomycin concentrations *a priori* (no observed concentrations included) or with Bayesian forecasting (using concentration data). Predictive performance was measured with relative bias (rBias) and relative root mean squared error (rRMSE). Models were clinically acceptable if rBias was ±20%, and 95% CI included 0. No threshold was used for rRMSE. The influence of clinical factors on model performance was assessed with multiple linear regression.

Results. Data from 82 patients were used to evaluate 12 vancomycin models. The Goti model was the only clinically acceptable model with both *a priori* (rBias 3.4%) and Bayesian forecasting (rBias 1.5%) approaches. Bayesian forecasting was superior to *a priori* prediction, improving with the use of more recent concentrations. Three models were clinically acceptable with Bayesian forecasting. Dialysis status ($p<0.001$), sex ($p=0.007$) and Sequential Organ Failure Assessment Score ($p=0.005$) significantly influenced the performance of the Goti model.

Discussion. The Goti, Llopis-Salvia and Roberts models are clinically appropriate to inform vancomycin dosing in critically ill patients. Implementing the Goti model in dose prediction software could streamline dosing across both ICU and non-ICU patients, considering it is also the most accurate model in non-ICU patients (Broeker et al, 2019).

Broeker A et al (2019) Clin Microbiol Infect 25:1286e1-e7. Rybak MJ et al (2020) Am J Health Syst Pharm 77:835-64.

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Circulating intestinal fatty acid binding protein and gastrointestinal toxicity in Russell's Viper envenomation

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Introduction. Abdominal pain is known to be an early clinical predictor of severe systemic Russell's Viper (RV) envenomation and is often associated with the later development of coagulopathy and neurotoxicity. The mechanism of abdominal pain still remains unknown but might be due to intestinal microvascular endothelial damage. This study hypothesised gut-toxicity could be detected using a novel biomarker Intestinal Fatty Acid Binding Protein (IFABP)and that severe gut-injury leads to gut-barrier failure, translocation of gastrointestinal microorganisms, associated sepsis, with a possible exacerbation of snake-bite severity, including worsening effects on renal function, previously attributed to direct venom effects.

Methods. Serial plasma samples of 16 RV envenomation with abdominal pain, 15 RV envenomation without abdominal pain and 25 healthy controls were retrospectively assayed for IFABP (Hycult Biotech, Netherlands). Samples were also assayed for procalcitonin as a sensitive marker for gram negative sepsis and serum cystatin C (CysC) as a sensitive early marker of renal injury.

Results. The median peak IFABP for healthy controls was 270.1pg/mL (IQR 153.5 – 558.0pg/mL) compared to median peak of all RV envenomation 3703.0pg/mL (2250.1 – 13702.0pg/mL) ($p<0.001$). Median peak IFABP with abdominal pain was 3801.4pg/mL (2080.5 – 22446.3pg/mL) compared without abdominal pain 3696.6pg/mL (2280.3 – 4664.7pg/mL) ($p=0.999$). Median procalcitonin levels was elevated 14.00ng/mL (IQR 5.4 – 36.9 ng/mL) with a level >2ng/mL indicative of severe sepsis and correlated with I-FABP ($r= 0.553$, $p=0.006$, $n=23$). Median serum CysC on RV samples was 1.47mg/L (IQR 0.87 – 1.84mg/L) and significantly correlated with IFABP ($r = 0.72$, $p=0.037$, $n=9$).

Discussion. I-FABP is significant elevated in patients with RV envenomation showing that enterocyte damage occurs. However, there was no difference in I-FABP between patients with abdominal pain and without suggesting that there is another cause for abdominal pain in RV envenomation. IFABP did correlate with markers of sepsis (procalcitonin) and end organ damage (serum Cystatin-C) which suggests that enterocyte damage resulting in translocation of microbial associated molecular patterns (MAMPs) contributes to RV envenomation associated sepsis.

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Quality analysis of commercially available *Annona muricata* leaf products

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Introduction. *Annona muricata*, also known as soursop, graviola and guanabana is a plant traditionally used for the treatment of cystitis, headache, insomnia and cancer. More recently, interest in the use of *Annona muricata* by people living with cancer has increased and led to the manufacture of *Annona muricata* products that are easily accessed via online shopping.

Aims. The aim of this study is to evaluate the quality and safety of selected commercially available *Annona muricata* products.

Methods. Five products were selected via popular online shopping sites. Each product was assessed for indicators of quality and safety including: weight variation, quantification of the bioactive constituent annonacin, microbial and heavy metal analysis. Annonacin was evaluated and quantified by thin layer chromatography (TLC), high performance liquid chromatography (HPLC), liquid chromatography mass spectroscopy (LCMS), Nuclear Magnetic Resonance (NMR). Microbiological analysis was carried out by a National Association of Testing Authorities, Australia (NATA) accredited pharmaceutical analytical company. Heavy metals were analysed inductive coupled plasma mass spectrometry (ICP-MS).

Results. Of the five products analysed, there was a high variation of annonacin concentration. One of the products had a total aerobic microbial count above the United States Pharmacopoeia (USP) limit, the product was predominantly contaminated by *Bacillus subtilis*. Two of the products had a lead concentration above the USP permissible limit.

Discussion. The variation in product quality and safety indicators raises significant considerations for clinicians and people living with cancer about the safe use of traditional medicine products.

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Apocynin ameliorates cigarette smoking-induced loss of skeletal muscle mass and function by preserving protein synthesis signalling.

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Introduction. Cigarette smoking (CS) is the major risk factor for the development of Chronic Obstructive Pulmonary Disease (COPD) and comorbid skeletal muscle dysfunction. Up to 40% of patients with COPD suffer from skeletal muscle wasting and dysfunction, but the mechanisms underlying this is not fully understood.

Aim. To examine the effect of NADPH oxidase inhibition using apocynin, on CS-induced skeletal muscle dysfunction.

Methods. Male BALB/c mice were exposed to either room air (sham) or CS generated from 9 cigarettes per day, 5 days per week for 8 weeks with or without apocynin (5mg·kg^{-1}·day^{-1}, *i.p.* injection) administration. C2C12 myotubes exposed to either hydrogen peroxide (H_2O_2, 0-100µM) or water-soluble cigarette smoke extract (CSE, 0-100%) with or without apocynin (500 nM), was set up as an experimental model *in vitro*.

Results. In mice, 8 weeks of CS exposure resulted in lung inflammation and muscle dysfunction evidenced by a 10% loss in mass and 54% loss (both $p<0.01$, n=8) in contractile function of tibialis anterior. The muscle dysfunction is likely to be attributed to a combination of altered myogenic homeostasis and protein oxidation. These effects were largely ameliorated by apocynin administration ($p<0.05$, n=8). In C2C12 myotubes, exposure to H_2O_2 or CSE led to myofiber wasting in a concentration-dependent manner. The myofiber wasting was associated with altered protein synthesis signalling marked by ~50% loss in muscle-derived Insulin-like growth factor (IGF)-1 and 1.5-fold increase in myostatin expression ($p<0.01$, n=3) without muscle inflammation. Apocynin treatment completely attenuated the CSE-induced NADPH oxidase 2 expression, preserving muscle-derived IGF-1 expression and downstream mTOR signaling pathway, thereby protecting the myofibers against wasting ($p<0.01$, n=3).

Discussion. Attenuation of oxidative stress by apocynin was able to preserve muscle mass and function against the detrimental effects of CS exposure. Targeting CS-induced oxidative stress may be a novel pharmacological strategy to treat both the pulmonary and extrapulmonary manifestations of COPD.

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Spatial reference memory impairment is augmented in hypertensive mice following stroke

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Introduction. Cognitive impairment is an aging-related disorder that can arise as a result of cardiovascular pathology or cerebrovascular injury. Considering the aging of our population, the incidence of cognitive impairment is thus expected to rise. Hypertension is a major modifiable risk factor for stroke and cognitive impairment, but it is unclear whether it may worsen post-stroke cognitive outcomes.

Aims. This study aimed to determine the effect of hypertension on post-stroke cognitive outcomes.

Methods. C57BL/6J mice (n=80) were randomly assigned to receive chronic infusion of either saline or angiotensin II (0.7 mg/kg/day s.c.) via osmotic minipump. Systolic blood pressure was measured weekly by tail-cuff. Seven days after minipump implantation, mice underwent either sham or photothrombotic stroke surgery targeting the prefrontal cortex, an area that is important for spatial reference memory. A separate cohort of mice underwent daily testing using the Barnes maze test from days 22 to 26. Results. Angiotensin II increased systolic blood pressure (saline, 118±1 mmHg vs. Ang II 149±2 mmHg; $P<0.05$) but this was not affected by stroke (Ang II + sham, 151±4 mmHg vs. Ang II + stroke 148±2 mmHg). In the Barnes maze, hypertensive mice that received stroke surgery took longer to enter the escape hole when compared to other groups (escape latency: Ang II + stroke 142.2 s vs. Ang II + sham 124.6s vs. saline + stroke 109.9 s vs. saline + sham 105.2 s), suggesting that they have poorer spatial reference memory.

Discussion. These findings indicate that the combination of hypertension and stroke resulted in more severe spatial reference memory impairment and brain injury than either insult alone.

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Relaxin inhibits matrix remodelling of collagen gels by asthmatic fibroblasts

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Introduction. Lung fibrosis represents an aspect of the dysregulated wound healing response to chronic lung injury and is a key feature of asthma. Inhaled glucocorticoids are used to reduce inflammation in asthma but do not affect airway remodelling. Relaxin (RLX) is a peptide hormone with well-known anti-fibrotic effects (Royce et al., 2014). Whether RLX directly inhibits remodelling by human airway fibroblasts is unknown. The aim of this study was to test the effects of RLX on collagen gels seeded with fibroblasts from non-asthmatic and asthmatic patients. Reductions in gel area ("contraction") occur over hours to days, are increased by the pro-fibrotic mediator TGFβ and can be used as a measure of remodelling of the surrounding matrix.

Aims. To compare the effects of RLX, the anti-fibrotic drug pirfenidone and the anti-inflammatory steroid dexamethasone on collagen gel contraction mediated by non-asthmatic and asthmatic fibroblasts.

Methods. Non-asthmatic and asthmatic fibroblasts were serum-starved for 72h before experiments. Cells were trypsinized and resuspended at $0.5x10^6$ cells/mL in 4X DMEM and combined with collagen solution (1 part cells: 3 part collagen). This mixture was transferred into 24-well culture plates (500 µL/gel). Once set, gels were dislodged into 6-well culture plates and suspended in 3 mL 1xDMEM for up to 72 h. Gels were treated with TGFβ (2ng/ml) in the absence and presence of RLX (100nM), and compared to pirfenidone (500µM) and dexamethasone (100nM).

Results. Gels seeded with asthmatic fibroblasts contracted more than gels seeded with non-asthmatic fibroblasts, and this contraction was further increased by TGFβ1. Both RLX and pirfenidone inhibited TGFβ1-mediated contraction of collagen gels seeded with non-asthmatic fibroblasts, but RLX was markedly more potent and only RLX was effective in reducing collagen gel contraction from asthmatic fibroblasts. Dexamethasone was unable to inhibit collagen gel contraction, consistent with its primary use in asthma to reduce inflammation rather than fibrosis.

Discussion. RLX opposes the increased contraction of collagen gels by TGFβ1 more effectively than pirfenidone or dexamethasone. These promising results, also evident in gels seeded with asthmatic fibroblasts, support the potential role of RLX as a potent anti-fibrotic treatment in asthma.

Royce et a (2014) Clin Exp Allergy 44: 1399-1408

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Anandamide-induced vasodilatation in normotensive and hypertensive rats

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Introduction. Anandamide, an endogenous agonist of cannabinoid CB_1 receptors and transient receptor potential vanilloid 1 (TRPV1) channels, can inhibit vasoconstriction and decrease blood pressure by modulating sympathetic and sensory neurotransmission. The effect of anandamide action on vascular tone in hypertension is unclear.

Aims. To examine the effect of anandamide on arterial tone in 16-week-old male normotensive Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR) and ascertain its mechanism(s) of action *in vivo*.

Methods. In anaesthetised rats (2% isoflurane mixed with O_2; spontaneous inhalation via nose cone), intravital microscopy was used to investigate mesenteric arterial diameter. Anandamide concentration-response curves were generated in U46619-constricted (300 nmol/L) arteries in the absence and presence of i) the CGRP receptor antagonist, BIBN 4096 (1 µmol/L); ii) the fatty acid amide hydrolase (FAAH) inhibitor, URB937 (100 nmol/L) to inhibit anandamide degradation; and iii) capsaicin (10 µmol/L) to desensitise sensory nerves. Similar experimental protocols were performed in isolated mesenteric arteries via wire myography.

Results. Anandamide caused concentration-dependent relaxation in arteries from both rat groups. Maximum relaxation (Rmax) was greater in WKY rats than in SHR (89±9 vs. 47±5%, n=7 and 6, respectively; $P<0.05$). URB937 enhanced anandamide-mediated vasodilatation in SHR only (Rmax, 89±6%, n=5; $P<0.05$). Capsaicin abolished anandamide-induced relaxation in both groups (Rmax, 1±6 and 11±8%, respectively, n=5; $P<0.05$) while BIBN 4096 had no effect. In contrast, *in vitro* anandamide relaxed pre-constricted mesenteric arteries isolated from WKY rats and SHR with similar potency and efficacy (pEC_{50}, 6.22±0.04 vs. 6.31±0.05, respectively) and URB937 had no appreciable effect on anandamide-mediated relaxation. Capsaicin inhibited anandamide-mediated relaxation *in vitro* and its inhibitory effect was more marked in SHR than WKY rats (63-fold vs. 23-fold decrease in pEC_{50}, respectively; $P<0.05$).

Discussion. Compared to WKY rats, anandamide-mediated relaxation was impaired in SHR *in vivo*, possibly due to a higher level of expression and/or activity of FAAH in SHR arteries. Although the inhibitory effects of capsaicin initially suggest the involvement of sensory nerve activation in anandamide-mediated vasodilatation, the absence of inhibition following BIBN 4096 treatment suggests that sensory nerve-derived CGRP is not involved in anandamide-mediated vasodilatation *in vivo*. In contrast to arteries in the intact circulation, FAAH activity may be limited in isolated arteries.

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The pro-resolving lipid mediator lipoxin A_4 protects against inflammation in diabetic cardiomyopathy

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Introduction. Failure to resolve inflammation may contribute to the progression of diabetic cardiomyopathy. We have previously demonstrated that the pro-resolving lipid mediator lipoxin A_4 (LXA_4) attenuates the development and progression of diabetes-induced atherosclerosis, but its impact on diabetic hearts has not been fully explored.

Aim. To test the hypothesis that LXA_4 could attenuate cardiac inflammation in diabetic mice.

Methods. 6-week-old male $ApoE^{-/-}$ mice were followed for 16wks after streptozotocin (55mg/kg/day i.p. for 5 days)-induced diabetes or vehicle control. Mice were randomly allocated to receive either LXA_4 (5µg/kg) or vehicle (0.02% ethanol) via i.p. injections twice/week for the final 6wks. At the end of the study, mice were culled with an overdose of Sodium Pentobarbital (100mg/kg), organs harvested for *ex-vivo* analysis.

Results. Diabetic mice displayed elevated HbA1c levels, retarded body weight gain, increased infiltration of macrophages in the myocardium and elevated expression of M1-like macrophage marker (Table). Interestingly, administration with LXA_4 significantly decreased the expression of M1-macrophage maker m*S100A9* and inflammatory marker m*Il-1β*. The macrophages content was no longer evident in the diabetic mice treated with LXA_4.

	Non-diabetic mice		Diabetic mice	
	Vehicle	LXA_4	Vehicle	LXA_4
Body weight (g)	32.06±1.78 (n=17)	30.63±2.50 (n=8)	25.71±1.38**** (n=7)	25.57±2.51**** (n=7)
HbA1c (%)	4.55±0.58 (n=15)	4.56±0.52 (n=15)	11.81±1.10**** (n=7)	11.14±1.40**** (n=7)
Macrophage content (No./0.43mm^2)	11.73±4.04 (n=13)	12.39±4.31 (n=12)	18.18±7.82** (n=9)	14.08±3.36 (n=9)
m*S100A9* (fold increase)	1.00±1.92 (n=17)	0.49±0.31(n=7)	4.78±6.40** (n=7)	0.54±0.32$^{\#}$ (n=7)
m*Il-1β* (fold increase)	1.00±0.95 (n=17)	0.92±0.37 (n=7)	1.59±1.34 (n=7)	0.42±0.13$^{\#}$ (n=7)

**p<0.001, ****p<0.0001 vs non-diabetic + vehicle; $^{\#}$p<0.05 vs diabetic + vehicle, (2-way ANOVA, Fisher's post-hoc for multiple comparisons).

Conclusion. LXA_4 may reduce inflammation by promoting the resolution of inflammation in the diabetic heart, thus supporting the development of an LXA_4 based therapy to improve the outcome for patients with diabetic heart diseases.

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Ebselen prevents cigarette smoke-induced cognitive impairment in mice.

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Introduction. Chronic obstructive pulmonary disease (COPD) is a major, incurable health burden, that is currently the 3rd leading cause of death globally, with cigarette smoking (CS) being the leading causative factor. People with COPD often suffer from cognitive dysfunction, which reduces their quality of life and increases their risk of death. However, the mechanisms underlying these impairments are unknown. It is believed that the increased inflammation and oxidative stress in the lungs may 'spill over' into the systemic circulation, reaching and damaging other organs such as the brain, leading to extra-pulmonary manifestations, such as cognitive dysfunction.

Aims. To determine whether chronic CS exposure causes neuroinflammation and cognitive dysfunction in mice and if so, to define the role of oxidative stress in these processes.

Methods. We assessed both working (novel object recognition [NOR] test) and spatial (spontaneous Y-maze [sY-maze] test) memory as well as hippocampal microglial numbers, morphology (ionized calcium binding adaptor molecule-1 immunohistochemistry) and oxidative protein carbonylation in male BALB/c mice exposed to CS (9 cigarettes/day, 5 days a week) or room air for 8 weeks with co-administration (oral gavage) of either the glutathione peroxidase (Gpx) mimetic ebselen (10mg/kg) or vehicle (5% CM-cellulose).

Results. CS exposure caused significant hippocampal-dependent working (NOR; n=8; p=0.004) and spatial (sY-maze; n = 10-12; p=0.012) memory impairment. CS-exposed displayed an activated microglial profile that is not observed in sham mice (n=8; p=0.001). In addition, CS exposure increased brain protein carbonylation (n = 8; p = 0.003), indicative of a heightened oxidative stress. Ebselen completely prevented hippocampal-dependent memory loss in both the sY-maze (n=8-12; p=0.004) and NOR test (n=8, p= 0.003).

Discussion. Chronic CS exposure impairs hippocampal-dependent memory which was associated with neuroinflammation and oxidative stress. By targeting oxidative stress, ebselen ameliorated CS-induced neuroinflammation, which completely prevented memory loss. Ebselen may be a novel therapeutic treatment for the neurocognitive impairments associated with COPD.

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The psychosocial and work related impacts of the COVID-19 pandemic on Australian Pharmacists

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Introduction. The COVID-19 pandemic has led to unprecedented changes in the delivery of pharmacy services with pharmacists understanding they have an important role to play in the delivery of healthcare during this time. A changing work environment, and uncertainty are contributing to the psychological burden being felt by health professionals during the pandemic.

Aims. To determine the prevalence of burnout and the psychosocial and work related effects of the COVID-19 pandemic on Australian pharmacists.

Methods. A national survey was distributed to pharmacists throughout Australia using convenience sampling through social media and pharmacy professional organisations during April and June 2020. Burnout scores were calculated using the Maslach Burnout Inventory (MBI) and descriptive statistics were used to determine the effect of COVID on various work related and social variables.

Results. A total of 647 responses were received that contained full datasets to be analysed. Almost 40% of respondents were community pharmacists, 42.4% were hospital, 3.3% were from areas other than hospital/community pharmacy and 14.4% worked in a combination. The mean burnout scores for each of the burnout categories are presented in the table and indicate a higher degree of burnout than has been previously reported (Durham et al 2018). There were 35% of pharmacists that reported an increased workload during COVID however only 17.8% had directly cared for a COVID positive patient. Medicines supply issues, an increase in workload and patient incivility were rated as factors most likely to affect pharmacists at work. Pharmacists were somewhat concerned about their own health or the health of their families as a result of their work and 87.2% reported that COVID-19 had affected their personal life.

MBI category	Mean score	Standard deviation
Emotional exhaustion	28.5	13.39
Depersonalisation	7.98	5.64
Personal accomplishment	36.58	7.56

Discussion. The COVID -19 pandemic has had a profound effect on the work and lives of Australian pharmacists, with many pharmacists experiencing burnout during this time.

1 Durham ME et al (2018) Am. J. Health Syst. Pharm; 75:S93-100.

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Do pharmacy practice standards effectively describe behaviour? Reviewing practice standards using a behavioural specificity framework

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Introduction. Guidelines and practice standards should express behaviours explicitly so they can be interpreted, enacted and measured with ease. Behavioural specificity within pharmacy practice standards has not been quantified. No behavioural specificity frameworks have been adapted to evaluate behaviours described in practice standards. The AACTT framework specifies behaviour in terms of the: Action to be performed, Actor who performs the action, Context where the action occurs, Target who the action is performed with/for and Time when the action is performed (AACTT).[1] Adapting this framework to evaluate practice standards may highlight areas for improvement.

Aims. 1) Develop a process for applying the AACTT framework to the evaluation of behaviours in a practice standard. 2) Determine if behaviours described in the Australian Professional Practice Standards for pharmacists specify Action, Actor, Context, Target and Time (AACTT).

Methods. Two researchers independently reviewed the scope and structure of the practice standards. Two researchers identified and extracted the action statements (behaviours) verbatim and applied definitions for the AACTT criteria to each behaviour. Each statement was coded based on whether AACTT criteria were met. Through an iterative process, researchers modified and developed definitions further, curated examples and developed a codebook. Final definitions were then applied to all action statements by one researcher and 20% check by a second.

Results. A process and codebook to apply AACTT criteria to evaluate practice standards were developed. Application of the framework identified 768 independent behaviours, of which 714 (93%) required further clarification of the action, none specified an actor, 25 (3%) specified context, 131 (17%) specified target and 88 (11%) specified time.

Discussion. The successful development of a novel reproducible process and codebook to evaluate behavioural specificity could be used by practice standard and guideline developers in the pharmacy profession, and beyond, to improve interpretability, useability and adherence to these documents.

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Expanding primary health care pharmacy practice in Aotearoa New Zealand: testing theories using a realist-informed approach

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Introduction. Worldwide, primary health care pharmacy roles are expanding, often to include the delivery of more patient-facing services, wider scopes of practice, and different workplace settings. Pharmacists in these roles operate within an established milieu that influences their ability to deliver on expanded offerings. This consequently affects service user outcomes and the ability to meet health policy expectations.

Aims. To test and refine theories explaining the successful expansion of pharmacist roles in Aotearoa New Zealand primary health care.

Methods. Semi-structured interviews were conducted with 43 stakeholders between 2017-2019 using realist-informed methods. Stakeholders represented the pharmacy, medicine, nursing, and consumer sectors, and included policy, practice, education, and advocacy perspectives. Transcripts were coded thematically using NVivo and concepts were extracted from these codes for iterative testing against theories that aimed to explain what works to enable successful expansion of these roles.

Results. Theories emerging from this work suggest five key mechanisms influence the development of expanded roles and services by pharmacists. These are: the level of optimism about offering new services, the pharmacist's approach to managing risk, judgements regarding financial incentives, ease of implementation, and perceptions regarding local service opportunities. Each mechanism has a range of contexts 'triggering' it. If the optimal context is missing, this prevents effective expansion of pharmacist roles.

Discussion. These interviews set the scene for two projects. One investigates how changes in community pharmacy in Aotearoa New Zealand likely influence health and health service outcomes. The other explores the contexts in which roles, such as that of the general practice pharmacist, successfully operate and the mechanisms influencing success. Findings will next be explored through case studies with practice pharmacists, their colleagues, and service users.

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Interprofessional collaboration of general practice pharmacists in the Australian Capital Territory

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Introduction. In the last decade, the inclusion of pharmacists into general practices has expanded in Australia. However, there is a paucity of research to explore interprofessional collaboration between the pharmacist and other members of the general practice health care team after the addition of pharmacists.

Aims. To investigate interprofessional collaboration between general practice pharmacists and General Practitioners (GPs) and Other Health Professionals (OHPs), following the introduction of pharmacists into general practice.

Methods. A collaborative care survey, largely based on existing validated tools, was used to explore (i) professional interactions, (ii) relationship initiation, (iii) exchange characteristics (role specification and trustworthiness), and (iv) collaborative care domains. Surveys were distributed to general practice pharmacists (n=8), GPs (n=65), and OHPs (n=40) in eight general practices in the Australian Capital Territory. Pharmacists rated their collaborative relationship with GPs, whereas GPs and OHPs rated their relationships with general practice pharmacists.

Results. Fifty-six participants (8 pharmacists, 31 GPs, 17 OHPs) completed the survey. Almost 60% of the respondents were females, and 41% were aged more than 50 years. Total survey scores (mean±SD as %, where higher percentages represent more advanced collaboration) were 83±3 for pharmacists, 80±3 for OHPs, and 74±4 for GPs. Pharmacists rated higher scores (mean ±SD) for relationship initiation with GPs (4.4±0.5) compared to GPs' (3.0±1.0) scores for relationship initiation with pharmacists ($P < 0.05$). OHPs reported higher scores for exchange characteristics (4.8±0.4) towards pharmacists compared to GPs' scores for the same (4.3±0.5) ($P < 0.05$).

Discussion. Overall, the results indicate that pharmacists were positively interacting with both GPs and OHPs after commencing their role in the general practice team. The interdependence of roles and trust towards general practice pharmacists appeared to be greater with OHPs than GPs.

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Pharmacists' roles in supporting people living with severe and persistent mental illness: a systematic review

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Introduction. People living with severe and persistent mental illness (SPMI) experience poorer physical health, often due to barriers accessing health care services. Pharmacists may play a significant role in improving physical and mental health for people living with SPMI, through optimising medicines use, improving medication adherence and providing education and counselling. However, little is known about pharmacists' current practices when providing services to this population nor the impact of such services on consumer-related health outcomes.

Aims. To systematically review the nature and impact of pharmacist-led services for people living with SPMI.

Methods. Medline, Embase, PsycINFO, CINAHL, Web of Science, Scopus, Cochrane Library, IPA and PQDT were searched for relevant publications. Studies published between January 1990 – April 2020 in English exploring pharmacist-led services for people living with SPMI were included.

Results. Thirty-six studies were included across various settings such as hospitals, community mental health centres and pharmacies. Schizophrenia was the most common SPMI reported by consumer participants (n=20), followed by bipolar disorder (n=6). Studies were mainly conducted in Asia (n=11) or the United States (n=8). Pharmacist-led services involved multiple components, such as educating consumers (n=20), providing recommendations/feedback to healthcare professionals (n=17), providing follow-up, assessment and monitoring services (n=14) and medication management (n=13). Of the 25 studies that reported a clinical and/or drug-related outcome, all studies showed positive improvements and 21 showed significant improvements in at least one clinical and/or drug-related outcome. The acceptance rate of pharmacist recommendations by doctors (n=7) ranged from 50% to 94%.

Discussion. Multifaceted pharmacist-led services for people living with SPMI can improve clinical outcome(s) such as promoting adherence and reducing symptom severity and polypharmacy. Despite these improvements, most studies acknowledged the absence of appropriate sample sizes and study duration could affect the generalisability of findings. Hence, future research exploring the long-term impacts of pharmacist-led services for this population is warranted.

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Are Australian community pharmacists engaging in mental health promotion?

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Introduction. The role of community pharmacists in public health promotion is well established, yet, little is known about whether, and how, pharmacists promote mental health and wellbeing, or their opinions of this.

Aims. To explore pharmacists' knowledge and attitudes, and facilitators and barriers, towards promoting mental health and wellbeing in community pharmacies.

Methods. A national online cross-sectional survey using Survey Monkey© assessed respondents' views and their respective involvement in promoting mental health and wellbeing, including what this involved, how existing national campaigns, e.g. R U OK? were utilised and other associated factors. Data were collected between November 2019-January 2020; results were analysed using descriptive statistics.

Results. Surveys were completed by 85 pharmacists, with responses from all Australian states and Territories. Less than half (n=37) of pharmacists had completed some form of mental health training in the last five years. Pharmacist self-reported definitions of mental health promotion included providing support and education, creating a safe health environment; and referral to other organisations and campaigns. All respondents were aware of at least one major national mental health promotion campaign, such as beyondblue and R U OK? While most pharmacists agreed that the pharmacy setting was well placed to provide mental health promotion (n=80; 63.0%), 40% (n=34) of participants did not actively promote this topic in their workplace and prior mental health related training appeared to facilitate this.

Discussion. To our knowledge this is the first study which has explored the uptake of more proactive mental health promotion beyond medicines-based counselling within community pharmacies. While a small sample size, key gaps have been identified in how community pharmacists approach mental health promotion alongside potential enablers, e.g. prior mental health-related training. This warrants further attention, particularly in the current economic and social climate and emergent mental health impacts of the COVID19 pandemic.

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Translational studies in geriatric pharmacology: Contributing to the global challenge of ageing well

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Introduction. Older people are increasingly major users of medicines. This is because the population is ageing, with an increase in multi-morbidity in old age. Older people have much to gain from medicines but are also highly vulnerable to adverse effects. There is a need to consider ageing physiology, multi-morbidity, polypharmacy and global health outcomes important to older people in drug development, use and regulation.

Aims. My translational research program, policy work, teaching and clinical practice all aim to improve the understanding of and outcomes from medicines in older people.

Methods. Conduct pre-clinical, pharmaco-epidemiological, clinical and implementation research to understand the effects of medicines in old age, particularly in the context of polypharmacy and frailty.

Results. Major contributions include: (i) Development of the Drug Burden Index, a pharmacological measure of an individual's total exposure to medicines with anticholinergic and sedative effects. This has been validated in international pharmaco-epidemiologic studies as a predictor of functional impairment and other adverse geriatric outcomes, has been shown to cause reversible frailty in old age in our laboratory model and used as an intervention and an outcome in clinical trials. Drug Burden Index has been used in implementation studies in hospital and community settings as a clinical risk assessment tool; (ii) Understanding the clinical pharmacology of frailty. Translational studies have found differences in drug use, pharmacokinetics and pharmacodynamics in those who are frail according to objective measures, compared to robust older people.

Discussion. The Drug Burden Index applies principles of pharmacology to minimise reversible medication related functional impairment in old age. Understanding the clinical pharmacology of frailty allows frailty to be considered as a factor in personalised medicine. These concepts and others can inform policy and education on quality use of medicines in old age. This work has been undertaken in collaboration colleagues from many ASCEPT special interest groups and through mentoring others to build capacity in the growing field of geriatric pharmacology.

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Giving/taking/matching/diversifying/translating/amplifying – Is collaboration worth it?

Prof Tina Brock, Monash University

The future of health care is patient-centred and team-based. The future of health professions education is interprofessional and technology-enhanced. Tina Brock believes that collaborations – across scientific disciplines, between institutions of higher learning, with health systems, and with innovative industries – have the potential to transform health in populations worldwide. But they take a lot of time, effort, skill, and science to work effectively. And the frustration rate is high. So, let's talk about strategies for making collaboration worth it.

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Outcomes of discontinuing anticholinergic medications in people living with dementia: A systematic review

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Introduction: Anticholinergic medication use is common in people with dementia. The cumulative effect of taking anticholinergic medications includes deterioration in cognitive and physical functioning. Where the potential harm of such medications outweighs the possible benefit, discontinuation of the medication may be appropriate.

Aims: To examine the effects of discontinuing anticholinergic medications in people living with dementia on prescribing and clinical outcomes.

Method: We searched Ovid MEDLINE, Ovid Emcare, PsycINFO, Cochrane Library, Web of Science, Clinical Trials Registry, and the World Health Organization Registry from inception to the 23rd of April 2020. We included interventional and observational studies that examined the relationship between discontinuing anticholinergic medications and prescribing and/or clinical outcomes in people aged ≥18 years living with dementia. Two researchers independently screened abstracts and full texts for inclusion, conducted data extraction, and critical appraisal for risk of bias. Our primary outcomes of interest were the reduction/discontinuation of anticholinergic medications and the change in cognitive function. Secondary outcomes included clinical outcomes (e.g. quality of life, falls, frailty, etc.) and process outcomes (e.g. intervention fidelity). The protocol was registered on PROSPERO; CRD42020165950.

Results: The literature search identified 1,134 articles. We reviewed the full text for 118 articles, of which six studies were included for final analysis. All included studies were interventional; three randomised controlled trials and three prospective cohort studies. A high risk of bias was noted among the included studies. All six studies reported significant discontinuation or reduction of anticholinergic medication use defined by various anticholinergic drug scales after the intervention (e.g. comprehensive medication review). Two studies reported no change in cognitive function post-intervention. One study reported no change in participants' physical function, and one other study reported a significant reduction in the participants' behavioural and psychological symptoms of dementia.

Discussion: While discontinuing/reducing anticholinergic medications seems feasible, limited evidence exists regarding the clinical outcomes of discontinuing anticholinergic medications in people living with dementia. Future research is needed to understand the most effective interventions to reduce anticholinergic medication use.

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Utilising MedicineInsight to promote quality of care among Australians with dementia: a national general practice dataset

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Introduction. There is a well-recognised need to improve quality of dementia care in primary care, and to identify opportunities to inform interventions to improve care through optimisation of prescribing.

Aims. To describe the distribution of dementia diagnosis, including subtypes and medicines utilisation among individuals enrolled in the NPS MedicineInsight database.

Methods. A cross-sectional study was conducted using the MedicineInsight dataset, a large national general practice dataset which provides monthly longitudinal, de-identified, whole-of-practice data extracted from the clinical information systems of 665 consenting general practices, representing 8.2% of all general practices across Australia. We used data collected up to August 2019. We included participants with a dementia diagnosis documented by the general practitioner in the condition codes and in the diagnosis records. Medication data was obtained from the details of prescriptions for each participant to determine current medications and general medication histories.

Results. On preliminary analysis, 40,227 older adults (65 years and over) with dementia were identified; with a mean age of 85.7 years and 60.2% female. With respect to dementia subtypes, Alzheimer's disease was the most common subtype (28.7%), followed by Vascular dementia (10.5%) and Lewy body and Parkinson's disease dementia (2.3%). Over half (56.7%) of participants had no dementia subtype recorded. At the time of first dementia diagnosis, participants were prescribed, on average, 7.6±5.5 medications, and 68.7% were exposed to polypharmacy (≥5 medications). Less than a quarter (23.0%) of older adults with dementia were taking anti-dementia medications such as acetylcholinesterase inhibitors and memantine. Individuals with Alzheimer's disease were prescribed significantly fewer medications (7.0±5.1 medications) compared with people with Vascular dementia prescribed significantly more medications (8.4±5.8 medications, $p<0.001$).

Discussion. Preliminary findings suggest that the quality of care of Australians with dementia in general practice could be improved with regard to documentation of dementia and its specific subtypes.

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Older adult and caregiver attitudes towards deprescribing: a systematic review

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Introduction: Use of harmful and/or unnecessary medications in older adults is common and leads to considerable harm including adverse drugs reactions, hospitalisation and mortality. Deprescribing (or withdrawal) of these medications may be appropriate and result in potential health benefits. Engaging patients by understanding their attitudes towards deprescribing could increase the uptake of deprescribing recommendations in practice.

Aims: To conduct a systematic review of studies that have used the validated Patients' Attitudes Towards Deprescribing (PATD), revised PATD or the rPATDcog (version for people with cognitive impairment) questionnaire to capture older adults and caregiver self-reported attitudes towards their medications and deprescribing: 1) What is the willingness of older adults to have a medication deprescribed? 2) What characteristics and other factors are associated with willingness to have a medication deprescribed?

Methods: Databases (Medline via Ovid, Embase, Scopus, Web of Science, International Pharmaceutical Abstracts) were searched for original research articles from January 2013 to March 2020. Google Scholar was searched for citations related to the development and validation manuscripts of the PATD, rPATD and rPATDcog. The quality of articles was assessed using the SUrvey Reporting GuidelinE (SURGE). Two reviewers independently performed screening, data extraction and quality assessment.

Results: Of 310 abstracts, 111 full text references were screened. A total of 44 articles of 39 studies were included (range of sample sizes: 18-1981) in 17 countries with 9 language translations. Study settings included community, hospital, outpatient and residential aged care facility. Preliminary analysis found that 49-98% of patients were willing to stop one or more of their medications if their doctor said it was possible. The associations found between participant characteristics (e.g. age, gender, education level, number of medications and chronic health conditions) and willingness to deprescribe were inconsistent among the different studies.

Discussion: Most but not all patients would consider deprescribing if recommended by their doctor. Therefore, it is clinically worthwhile and important to communicate with each patient to understand and address individual enablers and barriers to deprescribing.

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Improving acute care for people with dementia: Dementia Cohort in Acute caRE settings study (D-CARE)

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Introduction. Older people living with dementia use acute healthcare services commonly. Up to 19% of older adults have a medication-related adverse event immediately after hospitalisation. Inappropriate polypharmacy is recognised as a major contributing factor to adverse outcomes. However, currently, there is limited evidence about the patterns of prescribing among inpatients with dementia.

Aims. To establish the first in-depth, Australian dementia inpatient cohort study, and to compare patterns of prescribing during hospitalisation.

Methods. This retrospective cohort study included consecutive inpatients living with dementia, aged ≥75 years, whose first hospitalisation was after 1st July 2016, to three hospitals in a single health district in New South Wales. Dementia was defined by documented diagnosis in electronic medical records and confirmed with ICD-10. Medication use on admission and discharge were extracted from patients' medical records. Descriptive analyses were conducted to report patient demographics, and the prevalence of polypharmacy and potentially inappropriate medications (PIMs) (using the 2015 Beers Criteria) at admission and discharge. Paired t-test and McNemar test were used to compare difference in polypharmacy and PIMS on admission and discharge.

Results. On preliminary analysis, 500 inpatients were included in this study. The mean age of the population was 86.0 ± 5.7 (SD), 56% (n= 279) were female and 32% (n= 162) were admitted under orthopaedics. On admission, polypharmacy was identified in 47.2% (n= 236) and PIMs exposure in 52.4% (n= 262) of participants. The total number of medications increased significantly at discharge (5.3 ± 4.2 Vs 6.71 ± 4.0, $p<0.001$) compared to admission. But there was no statistically significant change in prevalence of participants prescribed ≥1 PIM from admission to discharge ($p=0.401$).

Discussion. Among inpatients with dementia, almost half are exposed to polypharmacy and PIMs. Future studies are needed to evaluate prescribing patterns across services to identify targets for interventions.

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Tools to evaluate medication management for caregivers of people with dementia: a systematic review

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Introduction. Caregivers often undertake medication management for people with dementia without formal training. There is a need to evaluate medication management practices for caregivers of people with dementia to identify and address the complexities of medication management.

Aims. To identify tools that evaluate medication management for caregivers of people with dementia and appraise caregiver's involvement in aspects of medication management.

Methods. Database search was conducted in Medline, Embase, PsycINFO, Scopus and International Pharmaceutical Abstracts. Original studies written in English which included tools that evaluated aspects of medication management for caregivers of people with dementia were included. Medication management was defined as the selection, supply, monitoring/review and administration of medications.

Results. A total of 10 studies were included. Medication selection was assessed in six studies, supply and monitoring/review was captured in seven studies, with administration assessed in nine studies. Caregivers were commonly involved in decision-making for medication changes (77.1-86.8%), and in the ordering (55.9-86.0%) and collection (87.0-92.4%) of medications. Tools reported on medication monitoring/review through evaluating caregivers' ability to recognise adverse effects and understanding of when to contact medical providers regarding medication management for the person with dementia. Reported caregiver involvement in medication administration ranged widely (44-94.7%) between tools. Common challenges in medication administration were due to polypharmacy and dosage regimen complexity.

Discussion. Current tools capture specific aspects of medication management, with medication administration the most evaluated aspect of medication management. Future research is needed to develop a tool to holistically evaluate the complexities of medication management for caregivers of people living with dementia to minimise adverse events and reduce caregiver burden.

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Differential sleep/wake response and sex effects following acute suvorexant, MK-1064 and zolpidem administration in the rTg4510 mouse model of tauopathy.

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Introduction. Tau transgenic rodent models of tauopathy display prominent sleep/wake disturbances, with a marked hyperarousal during their active phase. Hence, pathological tau may alter sleep/wake regulation.

Aims. The present study was designed to examine the sleep wake phenotypes of 6-6.5-month-old male and female rTg4510 mice following the acute administration of either 50 mg/kg suvorexant, a dual orexin receptor antagonist, 30 mg/kg MK-1064, a selective orexin receptor 2 antagonist, or 10 mg/kg zolpidem, a GABAA receptor positive allosteric modulator, using polysomnographic recordings.

Methods. rTg4510 transgenic mice and WT littermate controls were used. Polysomnography data was recorded from surgically implanted mice for 23 hours following drug or vehicle treatment using "Somnivore" (Allocca et al, 2019).

Results. Suvorexant exclusively promoted REM sleep in male and female rTg4510 mice, without affecting hyperarousal or NREM sleep. On the other hand, MK-1064, attenuated the hyperarousal phenotype of male rTg4510 mice by decreasing wake and increasing NREM sleep. By contrast, female rTg4510 mice exhibited a blunted response to MK-1064 compared to males. Zolpidem decreased wake and REM, whereas it increased NREM sleep equally in both male and female rTg4510 mice. Of the three compounds, MK-1064 appeared to promote the most physiologically relevant sleep with regard to NREM and REM sleep architecture.

Discussion. Our data indicate that pathological tau accumulation does not significantly alter the ability of tautransgenic mice to respond to sleep-promoting drugs. However, the sex differences observed in the sleep/wake response of rTg4510 mice to MK-1064, but not suvorexant or zolpidem, raises questions about therapeutic implications for the use of OX2R selective antagonists in human neurodegenerative disorders.

Allocca G et al, (2019) Front Neurosci. 13:207.

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Effects of β-estradiol on porcine distal ureteral contractility

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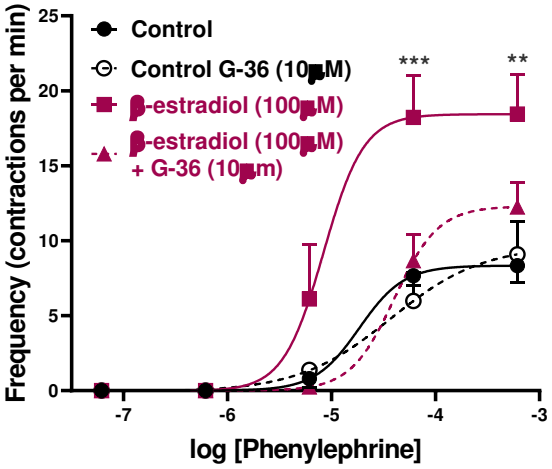
Introduction. The rate of urinary stone disease during pregnancy is increasing and associated with adverse birth outcomes (Sohlberg et al 2020). Estradiol has been shown to suppress bladder detrusor contractility (Valeri et al 2009).

Aims. The aim of this study was to investigate the effects of β-estradiol on phenylephrine-induced contractility in the porcine distal ureter.

Methods. Contractile responses of isolated porcine distal ureteral strips to phenylephrine were examined in the absence and presence of β-estradiol (100µM). The experiment was also performed in the presence of G-36 (10µM), a G protein-coupled estrogen receptor (GPER) antagonist.



Results. When subjected to increasing concentrations of phenylephrine, porcine ureteral tissues developed bursts of phasic contractions, and increasing agonist concentrations caused an increase in frequency and amplitude of phasic activity. In the presence of β-estradiol, the potency (pEC50) values of phenylephrine were unaffected (control vs β-estradiol, 4.97±0.23 vs 5.08±0.43). However, β-estradiol increased the frequency (refer to figure) and decreased the maximum amplitude ($p<0.001$, control vs β-estradiol, 257.9±24.3 vs 78.8±7.7 g/g) of these phenylephrine-induced contractions. G-36 (10µM) prevented the effects of β-estradiol on frequency of phasic contractions (refer to figure) but not the maximum amplitude ($p<0.001$, control G-36 vs β-estradiol and G-36, 231.2±23.4 vs 107.1±14.4 g/g).

Discussion. Our results suggest that estradiol increases the frequency of ureteral phasic contractions via GPER, while the mechanism through which estradiol decreases maximum amplitude is yet to be elucidated.

Sohlberg EM et al (2020) J Urol 203(5):957-961
Valeri et al (2009) Neurourol Urodyn 28(6):535-541

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Utilizing mini-G protein biosensors and BRET to profile orexin receptor pharmacology

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Introduction. The orexins, orexin A (OxA) and orexin B (OxB), are peptide agonists that bind to orexin receptor 1 (OxR1) and orexin receptor 2 (OxR2). OxA binds to both receptors with similar affinity while OxB exhibits substantially decreased affinity for OxR1. The orexin receptors have been reported to exhibit diverse G protein coupling behaviour that is tissue and cell-dependent. As such, characterization of the coupling capabilities of the receptors has remained somewhat controversial due to the large variability in observations dependent upon experimental variables.

Aims. We aimed to investigate the G protein activation profiles of the orexin system using mini-G protein biosensors in HEK293FT cells.

Methods. We utilized cutting-edge bioluminescence resonance energy transfer (BRET) technologies along with the newly developed G protein activation biosensors known as mini-G proteins (Wan et al, 2018) to monitor biosensor recruitment to activating GPCRs within live HEK293FT cells in real time.

Results. Mini-G protein recruitment was successfully monitored to both orexin receptors upon stimulation with either OxA or OxB using BRET. Both receptors coupled to multiple mini-G proteins with the most robust recruitment occurring with the receptors' prototypical G protein G_q (mGsq mini-G protein). Divergences in the strength of mini-G protein recruitment was observed between the receptors but also between OxA and OxB stimulation indicating ligand-dependent effects on mini-G protein recruitment.

Discussion. These findings demonstrate that the orexins exhibit the capacity for diverse G protein interactions within HEK293FT cells as demonstrated with the use of mini-G protein biosensors. Mini-G protein biosensors present a powerful tool to investigate the signalling capabilities of GPCRs.

Wan, Okashah, Inoue et al (2018) J Biol Chem 293:7466-7473

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Positive allosteric modulation of the M4 muscarinic acetylcholine receptor reverses MK-801 induced hyperlocomotion and sensorimotor gating deficits in mice.

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Introduction. The M_4 muscarinic acetylcholine receptor (mAChR) is a novel target for the treatment of schizophrenia (Gould et al., 2018), and can be selectively targeted with positive allosteric modulators (PAMs) to increase the sensitivity of the receptor to its endogenous neurotransmitter, acetylcholine, ACh. M_4 PAMs can enhance the affinity and/or efficacy of ACh and boost the cholinergic system. Through recent extensive medicinal chemistry efforts, a plethora of M_4 selective PAMs has been identified, with one particularly promising compound, VU0467154.

Aim. To pharmacologically assess the novel M_4 PAM, VU0467154, in recombinant systems overexpressing the human or the mouse M_4 mAChRs, and in two mouse models of psychosis.

Methods. *In vitro* assays were initially performed at the human and the mouse M_4 mAChRs. The degree of allosteric effect, i.e. cooperativity, between VU0467154 and ACh were quantified in [^{3}H]-N-methyl-scopolamine equilibrium binding, [^{35}S]-GTPγS binding and ERK1/2 phosphorylation assays. *In vivo* assays assessed the ability of VU0467154 (1-10mg/kg) to reverse MK-801-induced locomotor hyperactivity (LMA) and disruption of pre-pulse inhibition (PPI).

Results. Binding and functional interaction assays revealed that VU0467154 displayed high binding and functional cooperativity with ACh at the mouse M_4 mAChR. However, PAM effects were significantly smaller at the human M_4 mAChR. Excitingly, VU0467154 reversed the MK-801 psychotic-like effects in both LMA and PPI.

Discussion. This study validates VU0467154 as a M_4 PAM candidate that performed well in two drug-induced mouse models of psychosis, however also highlights high degree of species variability for the M_4 mAChR. Further medicinal chemistry efforts around this M_4 PAM may yield potential novel drug candidates for the treatment of Schizophrenia with improved efficacy for the human M_4 mAChR.

Gould et al (2018) Neuropharmacol 128: 492-502.

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Entry of valproate and lamotrigine into the developing brain

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Introduction. Pregnancy presents a serious challenge to epilepsy management, with long-term effects on children of epileptic mothers not well characterised. The antiepileptic drug valproate has been flagged for its dose-dependent teratogenicity, including potential deleterious effects on cognition several years after birth (Meador et al, 2013). Nevertheless, it remains in use, often in combination with other drugs such as lamotrigine, as the only means of seizure control for many pregnant women. Current treatment recommendations are based largely on expert opinion of clinicians and retrospective studies of pregnancy registers. Animal studies investigating mechanisms of placental transfer and developmentally regulated brain entry of antiepileptics are lacking and remain essential.

Aims. To determine the role of brain and placental barriers in modulating valproate and lamotrigine entry into the developing central nervous system.

Methods. The transfer of clinically relevant doses of valproate and lamotrigine from the plasma into the brain and cerebrospinal fluid (CSF) was estimated in Sprague-Dawley rats at three developmental stages (embryonic day (E) 19, postnatal day (P) 4 and adult) using intraperitoneal injections of radiolabelled drugs. Placental transfer was estimated at E19 using foetal/maternal plasma concentration ratios.

Results. Both valproate and lamotrigine entered the foetal brain at E19 to a higher level than at either postnatal age, however entry into the CSF was only higher for valproate at E19. The placental barrier provided a higher protection for lamotrigine (foetal/maternal plasma ratio was 20-30%) than valproate (foetal/maternal plasma ratio was 70-80%). At P4, the combination of valproate and lamotrigine had no significant effect on the entry of either drug into the brain.

Discussion. Higher drug entry into foetal circulation, CSF, and brain at E19 may contribute to the increased deleterious effects of valproate during pregnancy. No difference of valproate entry in the combination treatment at P4 indicates that limited risks remain when attempting to use lamotrigine to reduce the necessary valproate dose for seizure control.

Meador KJ et al (2013) Lancet Neurol 12:244-252.

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A Safety, Tolerability and Pharmacokinetic Study of a Novel Simvastatin Silica-Lipid Hybrid Formulation in Healthy Male Participants

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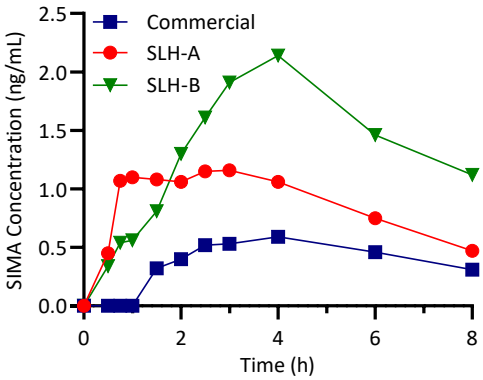

Introduction. Simvastatin (SIM) is clinically proven cholesterol-lowering drug which can reduce the risk of major cardiovascular events. However, SIM is poorly absorbed and undergoes extensive first-pass metabolism, resulting in a low oral bioavailability of less than 5%, after conversion to its active metabolite, simvastatin acid (SIMA)[1]. Silica-lipid hybrids (SLH) are a solid nanostructured lipid formulation proven to promote drug solubilisation, owing to a unique nanoporous matrix and high surface area[2]. Therefore, the current study aimed to reformulate SIM into a lipid formulation utilising SLH technology to enhance oral bioavailability.

Aims. To fabricate and optimize SIM encapsulated silica-lipid hybrids (SLH) to enhance absorption and bioavailability of SIM during a human *in vivo* pharmacokinetic study.

Methods. A randomised, cross-over, double-blinded, study design was used to evaluate the safety and pharmacokinetic profiles of SIM encapsulated SLH, compared to the commercially available formulation in healthy males aged from 19 to 67 years under fasting conditions.

Results. Pharmacokinetic analyses revealed that SLH technology enhanced the bioavailability of SIM up to 1.4-fold and importantly, up to 3.3-fold for SIMA, compared to the commercial formulation.

Discussion. The study indicated that SLH formulations were safe and well-tolerated when administered to healthy males, confirming the commercial potential of SLH to enhance the bioavailability of poorly water-soluble drugs, such as SIM.

[1]Tubic-Grozdanis, M (2008) Pharmaceutical Research. 25(7), 1591-1600
[2]Rao, S (2014) Nanomedicine, 9, 2745-2759

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Quantum dot nanomedicine formulations dramatically improve pharmacological properties and alter uptake pathways of metformin and nicotinamide mononucleotide in aging mice

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Orally administered Ag_2S quantum dots (QDs) rapidly cross the small intestine and are taken up by the liver.[1] Metformin and nicotinamide mononucleotide (NMN) target metabolic and aging processes within the liver. This study examined the pharmacology and toxicology of QD-based nanomedicines as carriers of metformin and NMN in young and old mice, determining if their therapeutic potency and reduced effects associated with aging could be improved.

Pharmacokinetic studies demonstrated that QD-conjugated metformin and NMN have greater bioavailability, with selective accumulation in the liver following oral administration compared to unconjugated formulations. Pharmacodynamic data showed that the QD-conjugated medicines had increased physiological, metabolic and cellular potency compared to unconjugated formulations (25× metformin; 100× NMN) and highlighted a shift in the peak induction of, and greater metabolic response to, glucose tolerance testing.

Two weeks of treatment with low dose QD-NMN (0.8 mg/kg/day) improved glucose tolerance tests in young (3 month) mice while old (18-month, 24-month) mice demonstrated improved fasting and fed insulin levels and HOMA-IR. High dose unconjugated NMN (80 mg/kg/day) demonstrated improvements in young mice but not in the old mice. After 100 days of QD (320 µg/kg/day) treatment there was no evidence of cellular necrosis, fibrosis, inflammation, or accumulation of QDs. Ag_2S QD-nanomedicines improved the pharmacokinetic and pharmacodynamic properties of metformin and NMN by increasing their therapeutic potency, bypassing classical cellular uptake pathways, and demonstrated efficacy when drug alone was ineffective in aging mice.

[1]Hunt, NJ et al (2020) ACS nano, 14(2), 1492-1507.

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Piperacillin/tazobactam plus tobramycin *versus Pseudomonas aeruginosa* in two *in vitro* infection models.

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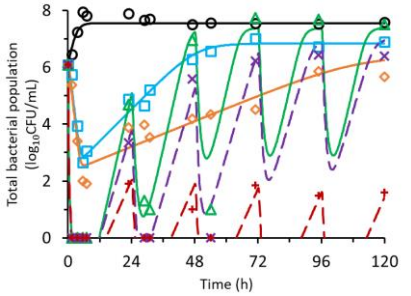

Introduction. *Pseudomonas aeruginosa* (Pa) is a common cause of nosocomial infections in various patient groups including the critically-ill. Critically-ill patients are particularly vulnerable to treatment failures, which may be due to sub-optimal antibiotic exposures.

Aims. Evaluate piperacillin-tazobactam (TZP) plus tobramycin (TOB) regimens simulating the PK of critically-ill patients with normal renal function.

Methods. A clinical isolate (MIC_{TZP} 4mg/L, MIC_{TOB} 0.5mg/L) from a critically-ill patient was evaluated in static concentration time-kill studies and subsequently studied in 120h dynamic *in vitro* infection models (IVM, inoculum 10^6 CFU/mL, performed in n=2 replicates). The IVM simulated the PK of TZP ($t_{1/2}$=1.5h) and TOB ($t_{1/2}$=3.1h), based on published population PK models. Regimens were: A. TZP 4g q4h as 0.5h infusions; B. TZP 24g/day as continuous infusion (CI); C. TOB 7mg/kg q24h as 0.5h infusions; A+C; and B+C. Total viable counts were determined at 13 time points and resistant bacteria quantified at 24h intervals. Mechanism-based modelling was performed (lines in figure).

Results. In the IVM (Figure), A provided <4 log_{10} CFU/mL initial killing, followed by regrowth close to control values by 72h. B provided 4.0-4.5 log_{10} initial killing, followed by regrowth close to initial inoculum by 96h. C and A+C provided extensive killing (up to 6 log_{10}) after each TOB dose up to 54h, with regrowth to control values and starting inoculum, respectively, and resistance emergence by 72h. B+C provided extensive initial killing and suppression of regrowth (to <2 log_{10}) and resistance emergence over 120h.

Discussion. Only TZP 24g/day CI + TOB suppressed regrowth and the emergence of resistance of Pa over 120h. As an intermittent regimen, the same daily dose of TZP with TOB resulted in sustained regrowth by 72h. Thus, the shape of the concentration-time curve was an important factor for achieving synergistic antibiotic effects with the combination treatment.

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The effect of caffeine intake on the renal clearance of calcium, sodium and creatinine in healthy adults

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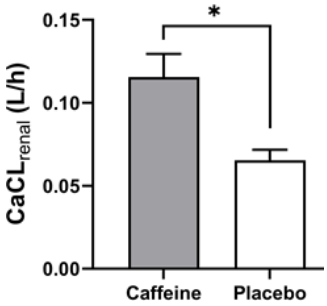

Introduction. Caffeine is the most widely used recreational drug in the world. Research has linked the consumption of caffeine to osteoporosis, believed to be due to enhanced bone resorption, owing to increased calcium excretion in the urine. However, urine calcium excretion may not necessarily reflect the true effect of caffeine on calcium status.

Aims. This study was conducted to examine the impact of caffeine consumption on the renal clearance of calcium ($CaCL_{renal}$), sodium ($NaCL_{renal}$) and creatinine ($CrCL_{renal}$) in healthy adults to provide mechanistic insight into the role of caffeine in calcium homeostasis.

Methods. In a randomised, double-blind, placebo-controlled clinical trial, participants (n = 24) consumed caffeine (2 x 100 mg gum) or placebo every 2 hours over a 6 hour treatment period. Blood and urine were collected at 0 (pre-dose), 1, 4, & 7 hours and analysed for calcium, sodium and creatinine concentrations. Pharmacokinetic parameters were determined using standard non-compartmental methods.

Results. Mean $CaCL_{renal}$, $NaCL_{renal}$ and urine output were 77%, 61% and 67% greater under caffeine conditions compared to placebo, respectively (p<0.05). In contrast, no significant difference between the treatments was seen for $CrCL_{renal}$ (p>0.05). Statistically significant relationships between $NaCL_{renal}$ and $CaCL_{renal}$ (R^2=0.47, p<0.0001) and $NaCL_{renal}$ and urine output (R^2=0.39, p<0.0001) were observed.

Discussion. For the first time, this study comprehensively examined the effect of caffeine on calcium economy and suggest that caffeine inhibits sodium reabsorption in the proximal convoluted tubule, thus increasing $NaCL_{renal}$, $CaCL_{renal}$ and urine output. Considering the lack of impact of caffeine treatment on $CrCL_{renal}$, these findings were in contrast with the previously proposed effect of caffeine on glomerular filtration rate through vasoconstriction of the afferent arteriole. This preliminary study provides mechanistic insight into the role of caffeine in osteoporosis and fosters the further investigation into safe consumption of caffeine with a focus on bone health.

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The effect of chronic polypharmacy and monotherapy on drug pharmacokinetics in mice.

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Introduction. Polypharmacy (use of ≥ 5 drugs) is common in older people and is associated with adverse outcomes. Understanding the impact of polypharmacy on pharmacokinetics could inform drug dosing in the clinical setting of polypharmacy.

Aims. To measure multiple drugs in serum and their metabolites in a preclinical chronic polypharmacy model[1].

Methods. From 12 to 21 months of age male C57BL/6 mice received therapeutic doses of drugs in their food/water. We administered one regimen of polypharmacy (simvastatin, metoprolol, oxybutynin, oxycodone, citalopram), and five of monotherapies of the same drugs and doses as in the polypharmacy treated group (n=~20/ group). At 15, 18, 21 and 24 months, blood was collected from the cheek vein. Drug levels were determined using the Shimadzu triple quadrupole mass spectrometer (MS) coupled with ultra high performance liquid chromatography (UHPLC)[1].

Results. At all ages, compared to metoprolol monotherapy, polypharmacy had significantly higher serum levels of metoprolol (2.8-6.0 fold increase, $p<0.05$) and alpha-OH metoprolol (2.5-3.8 fold increase $p<0.05$). The polypharmacy group had higher serum citalopram levels than the citalopram monotherapy (2.3-4.7 fold $p<0.05$). At 15 months, the polypharmacy group had significantly higher levels of oxycodone and noroxycodone than oxycodone monotherapy (1.6-4.8 fold $p<0.05$).

Discussion. Different drug levels were observed with different polypharmacy and monotherapy regimens. This model can be used to understand pharmacokinetics of drug interactions beyond drug pairs over time, as seen in chronic polypharmacy.

1. Mach J, Wang X & Hilmer SN (2020) [published online ahead of print, 2020 Aug 19]. *Fundam Clin Pharmacol*. 2020;10.1111/fcp.12602. doi:10.1111/fcp.12602.

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"The lesser of two evils": Consumer perspectives on opioid deprescribing and the development of opioid deprescribing guidelines

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Introduction. Deprescribing of opioids has been identified as a mechanism to facilitate judicious opioid use, however, it is often challenging to implement interventions and communicate deprescribing decisions to consumers. The development of opioid deprescribing guidelines may provide guidance and support on when and how to reduce or cease opioids. It is essential that the perspectives of consumers are explored and incorporated into guidelines to ensure that outputs are relevant and applicable for these key stakeholders.

Aims. This study aimed to explore the perspectives of Australian opioid consumers on opioid deprescribing and determine factors to be considered in the development of opioid deprescribing guidelines.

Methods. A purposive sample of twenty consumers utilizing opioids for pain were recruited. Semi-structured interviews were conducted, audio recorded and transcribed verbatim. Inductive thematic analysis was undertaken, followed by a framework analysis informed by Bandura's Social Cognitive Theory.

Results. Behavioral, cognitive and environmental factors influence consumers' attitudes and actions regarding opioid deprescribing. Significant barriers to opioid deprescribing include fears of pain and withdrawal effects, as well as perceived inadequacies of the healthcare system. Improved communication between healthcare professionals and consumers and affording consumers greater opportunity to engage in decision making were identified as avenues to improve the success of opioid deprescribing. Inductively derived themes align with Bandura's Social Cognitive Theory, suggesting that consumers' self-efficacy to engage in and persist with opioid deprescribing is a modifiable predictor of behavior which could be targeted in opioid deprescribing guidelines.

Discussion. For opioid deprescribing guidelines to be effective, opioid consumers need to feel empowered to engage in opioid reduction. The findings of this study enable a patient-centred approach for practitioners and guideline developers in creating recommendations to facilitate opioid deprescribing through targeting behavioral change.

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A meta-analysis on outcomes of medication misadventure among people with cognitive impairment or dementia

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Introduction. Factors such as multiple medication use and age can contribute to medication misadventure including medication errors (MEs), the use of potentially inappropriate medications (PIMs), and adverse drug events (ADEs) among people with cognitive impairment or dementia. However, it is not clear whether this translates to adverse health outcomes.

Aims. To investigate whether mortality and hospitalisation outcomes were associated with medication misadventure among people with cognitive impairment or dementia.

Methods. Ovid MEDLINE, EMBASE, IPA, CINAHL, and CENTRAL were searched from inception to December 2019. The primary outcomes of interest were mortality and hospitalisation associated with medication misadventure. The Joanna Briggs Institute Critical Appraisal Checklist was employed to assess the quality of included studies. Meta-analyses were conducted to find an association between exposure to PIMs and mortality/hospitalisation.

Results. The systematic review included 10 studies that reported the outcomes of mortality or hospitalisation

associated with medication misadventure, including PIMs (n=5), ADEs (n=2), a combination of MEs and ADEs (n=2), and drug interactions (n=1). Five studies examining the association between PIMs and mortality/hospitalisation were included in the meta-analyses. Exposure to PIMs was not associated with either mortality (odds ratio [OR]=1.36; 95%CI=0.79- 2.35) or hospitalisation (OR=1.02; 95%CI=0.83-1.26). In contrast, studies of cholinesterase inhibitors found that ADEs were associated with mortality and hospitalisation.

Discussion. The overall medication misadventure was not associated with mortality or hospitalisation in people with cognitive impairment or dementia, noting the limited number of studies, difficulty in controlling potential confounding variables, and that most studies focus on PIMs.

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Development and validation of explicit criteria for identification of potentially inappropriate prescribing for people with type 2 diabetes mellitus

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Introduction. Early detection and timely resolution of potentially inappropriate prescribing (PIP) prevents adverse outcomes and improves patient care. There are many tools to identify PIP that target older populations, but an explicit tool specifically designed to detect PIP among people with Type 2 Diabetes Mellitus (T2DM) is lacking.

Aims. This study aims to develop and validate the Inappropriate Medication Prescribing Assessment Criteria to Type 2 Diabetes Mellitus (IMPACT2DM); an explicit tool that can be used to identify PIP for people with T2DM.

Methods. Updated national and international guidelines for the management of T2DM and drug information software programs were used to generate potential items. The content of the IMPACT2DM was validated by 2 consecutive rounds of Delphi method. Physicians and clinical pharmacists experienced in the care of diabetic patients and authors of selected diabetes guidelines were invited to participate in the Delphi panel. Consensus was assumed if 90% (first round) and 85% (second round) of expert panelists showed agreement to include or exclude an item.

Results. A total of 95 potential items were generated from selected diabetes guidelines and drug information software programs. In the first and second round there were 12 and 7 Delphi panellists, respectively. At the end of the first round 27 items had ≥90% agreement and were directly included in the final tool; 19 items were considered not PIP and were excluded from the tool. The second round contained 49 items; of these 43 were included and 6 were excluded. The final IMPACT2DM contains 70 items categorized based on the type of PIP and arranged in terms of medical conditions and medication classes.

Discussion. IMPACT2DM is the first explicit tool specifically designed to identify PIP for adults with T2DM. The tool can be applied using information on medical charts and requires minimal or no clinical knowledge. IMPACT2DM can be used by researchers and clinicians to assess quality of diabetes care, improve medication selection, and educate health professionals who are working with diabetic patients.

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Duration of postoperative opioid use after hip or knee surgery: a systematic review and meta-analysis

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Introduction: Major orthopaedic surgery such as hip or knee surgery is associated with severe pain and has the potential to lead to persistent postoperative opioid use, which contributes to the global opioid crisis.

Aims: To conduct systematic review and meta-analysis to identify the proportion of adult patients taking opioids at 3-12 months after hip or knee surgery. Secondary objective was to determine risk based on preoperative opioid use status.

Methods: A systematic literature review was conducted using EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials and International Pharmaceutical Abstracts for articles published from 1st January 2009 to 24th June 2020. Only studies focusing on adults who underwent hip or knee surgery, with at least 3 months postoperative follow-up were included.

Results. In total 34 observational studies were included in the systematic review (n=865822). Of these, 16 reported hip surgery and 22 reported knee surgery. Six of them were conducted in veterans or military settings. In patients with hip surgery, postoperative opioid use was as follows: 3 months (21%, 95% CI [14%, 28%]), 6 months (18%, 95% CI [14%, 23%]), 9 months (22%, 95% CI [17%, 28%]) and 12 months (28%, 95% CI [26%, 29%]). In patients with knee surgery, postoperative opioid use was as follows: 3 months (23%, 95% CI [15%, 31%]), 6 months (20%, 95% CI [16%, 24%]), 9 months (5%, 95% CI [5%, 30%]) and 12 months (17%, 95% CI [4%, 31%]). Preoperative opioid users had higher opioid consumption at 3 months in patients with hip surgery (45% versus 4%) and knee surgery (55% versus 10%). Studies that were conducted in veteran or military setting reported higher proportion of postoperative opioid use compared to studies that were conducted in general population, especially for preoperative opioid user (higher than 50%).

Discussion: In patients who have hip or knee surgery, over 20% have persistent opioids use for longer than 3 months postoperatively and this may be sustained for over 12 months. Opioid naïve patients are less like to have continued postoperative opioid use compared to those who are opioid tolerant preoperatively. Clinicians involved in the care of these patients should be aware of this trajectory of opioid consumption after surgery and focus on deprescribing.

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Supporting medication adherence in the Maori and Pacific Islander community with type 2 diabetes in Australia

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Introduction. The Maori and Pacific Islander (MPI) population is significantly impacted by type 2 diabetes (T2D) and poor medication adherence has been identified as a factor that may lead to suboptimal health outcomes.[1] Research is required to understand influences on medication adherence in the MPI community.

Aims. To explore illness beliefs and medication adherence behaviours and identify strategies for supporting medication adherence in MPI population with T2D.

Methods. MPI patients prescribed medications for T2D were recruited through community organizations. Interviews were conducted by phone and videoconference and beliefs about diabetes and medications and the support needed for medicine use were collected. Interviews were recorded, transcribed verbatim and thematic analysis was applied utilizing Braun and Clarke methods. Themes were validated by the research team and triangulated with data collected from steering committee meetings.

Results. Of the 14 participants (8 Male and 6 Female), 6 were Fijian, 3 Samoan, 3 Tongan, 1 Maori and 1 Cook Islander. Participants ranged from 43 to 73 years. The main themes identified around diabetes were; faith and spiritual healing, food as a central part of life, privacy around health, shame and embarrassment about diabetes and stoic behaviour of men. Medicine related themes included; a preference for managing diabetes 'naturally', medicines damaging the body, cost of medicines, prioritizing family needs and religious offerings before medicines, low health literacy and language barriers. Participants expressed a lack of information and limited access to medicines support and proposed strategies favouring a holistic approach to medicines support, a preference for visually presented information, family involvement, translated resources and sharing experiences in a face-to-face environment.

Discussion. This study gives insight into the beliefs and behaviours around medication management for T2D in the MPI community in Australia. The research identifies important concepts and useful strategies to shape the development of resources to support the MPI community.

[1]Akbar H (2018) Socio-cultural context of managing T2DM in Aust. Pacific Islander women living in QLD, QUT

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Understanding the imprecision of precision medicine

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Introduction. Individualisation of drug therapy can facilitate efficacy whilst minimising toxicity. Various sources of routinely collected data (e.g. time of drug administration and blood sample collection) obtained from electronic health records are leveraged to inform optimal dosing strategies. Any inaccuracies in data used to predict individual drug exposure can potentially negate the benefits of precision dosing. However, the accuracy of these data and the effect of any discrepancies on the precision of optimal dosing strategies is unclear.

Aims. This research examines factors contributing to the variability in the accuracy of precision dosing strategies.

Methods. Quantitative and qualitative methods were used to assess the accuracy of the time of drug administration and blood sample collection. Monte Carlo simulation was used to predict the impact of discrepancies in time of drug administration on dose adjustments for vancomycin. In addition, the predictive performance (bias, precision) of population pharmacokinetic models used to predict drug exposure were evaluated. Observed concentration data and drug exposure (AUC) was compared with that predicted by population pharmacokinetic models.

Results. The median discrepancy between actual and documented administration times of antimicrobial agents was 16 min (range, 2-293 min). The observed discrepancies in vancomycin administration time was predicted to result in a different dose recommendation in 57.4% of cases (28.9% higher, 28.5% lower). Whilst blood collection times were accurately recorded, phlebotomists' high workload, insufficient communication between health professionals and workflow practices impede 'on-time' blood collections. The predictive performance of models for vancomycin and tacrolimus varied based on characteristics of the patient population.

Conclusions. Inaccuracies in data sources and models used to predict individual drug exposure can result in inappropriate dose recommendations. An understanding of the factors contributing to this variability can inform the design of interventions to improve the accuracy of precision dosing strategies.

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Novel BRET approaches to understand the complexities of endogenous GPCR function

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Introduction. Bioluminescence resonance energy transfer (BRET) is widely used to investigate protein or ligand interactions with membrane receptors and/or between cellular proteins. However, a fundamental limitation of current BRET techniques is the requirement for exogenous expression of fusion proteins, which precludes the direct application of this method to study endogenous protein interactions in their native cellular environments.

Aims. To use NanoBRET based techniques coupled with CRISPR/Cas9-mediated genome engineering to investigate G protein-coupled receptor function when expressed under endogenous promotion.

Methods. CRISPR/Cas9-mediated homology-directed repair was used to insert Nanoluciferase (Nluc) into native genomic loci of HEK293 and/or Hela cells, resulting in Nluc fused to proteins of interest. NanoBRET or Nluc complementation was used to investigate receptor function in population assays using a multilabel plate reader or at the single cell level via bioluminescence imaging

Results. We demonstrated that receptor ligand binding, receptor conformational changes, receptor internalisation, protein-protein interactions, and receptor trafficking could be monitored in live cells using proteins expressed under endogenous promotion. These approaches do not require over-expression of the proteins of interest, allowing natively expressed proteins to be studied and therefore representing improved models to investigate receptor function.

Discussion. Using CRISPR/Cas9-mediated genome engineering, NanoBRET can be used to observe various aspects of receptor function using GPCRs found under endogenous promotion. This overcomes a major limitation of existing BRET-based techniques and helps to better understand the influence of cellular context on receptor function.

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Rational design of dose individualisation strategies for 5-Fluorouracil (5-FU)

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Whilst there have been significant improvements in cancer treatment over the last few decades, it remains that 3/10 cancer patients will not survive past 5 years. These statistics not only reflect the consequence of tumour progression, but also the mortality associated with severe treatment-related side effects. In the setting of oncology, the standard approach for individualisation of therapy is based on body surface area (BSA) as a measure of body size. Yet, research has demonstrated that BSA-based dosing (as well as flat dosing) results in substantial variability in drug exposure and hence patient outcomes.

In other fields of medicine, dose individualisation strategies, including therapeutic drug monitoring (TDM), have been shown to significantly improve health outcomes, including shorter hospitalisation and reduced side effects. However, whilst the concept of dose individualisation has been proposed for the use of cancer therapeutics, the clinical application has not been widely realised. 5-FU represents the one of the few instances in which comprehensive randomised clinical trials examining the comparative outcomes of standard therapy and TDM-based dosing in oncology have been conducted. Despite this evidence, there remains no clear indication of the optimal dose individualisation strategy for 5-FU.

Population pharmacokinetic modelling and simulation provides an opportunity to examine different treatment strategies to provide an educated selection of the most appropriate dosing regimen, and prediction of its therapeutic success and safety in practice – a critical component for the quality use of medicines. This research program evaluates previously proposed TDM-based strategies for the management of 5-FU treatment in clinical practice. Whilst these dose individualisation strategies are associated with improvements in patient outcomes compared to standard treatment, they are still predicted to result in an unacceptably high rates of over-exposure, thereby increasing the risk of treatment-limiting toxicity. Exploring the foundational basis of these suboptimal outcomes, our group has identified an alternate dosing approach that has the potential to maintain efficacy whilst substantially reducing toxicity, ultimately improving therapeutic outcomes for cancer patients.

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Concomitant proton pump inhibitor use and survival in patients with advanced cancer treated with atezolizumab

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Introduction. Emerging evidence indicates that gut microbiota dysbiosis can reduce the effectiveness of immune checkpoint inhibitors (ICI). Proton pump inhibitors (PPIs) are known to induce gut microbiota changes. However, little is known on the effects of PPIs on outcomes with ICI therapy, and it has not been explored in urothelial cancer (UC) treatment.

Methods. Individual-participant data from the advanced UC trials, IMvigor210 (single-arm atezolizumab trial, n=429) and IMvigor211 (phase III randomised trial of atezolizumab versus chemotherapy, n=931) were pooled in a Cox proportional hazard analysis assessing the association between PPI use and overall survival (OS) and progression-free survival (PFS). PPI use was defined as any PPI administration between 30-days prior and 30-days after treatment initiation.

Results. Of the 1360 participants, 471 (35%) received a PPI within the 60-day window. PPI use was associated with significantly worse OS (HR 95%CI = 1.52 [1.27 – 1.83], P<0.001) and PFS (1.38 [1.18 – 1.62], P<0.001) with atezolizumab, but not chemotherapy (P>0.05). In the randomised cohort of IMvigor211, the OS treatment effect (HR 95%CI) of atezolizumab vs chemotherapy was 1.04 (0.81 - 1.34) for PPI users, compared to 0.69 (0.56 - 0.84) for PPI non-users (P[interaction]=0.013). Similar associations were noted in the PD-L1 IC2/3 population.

Discussion. The present study indicates PPI use is a negative prognostic marker in advanced UC treated with ICI therapy, but not chemotherapy. Further, the analysis suggests PPIs influence the magnitude of ICI efficacy, and this warrants further investigation.

Hopkins AM, Kichenadasse G, Karapetis CS, Rowland A, Sorich MJ. Concomitant Proton Pump Inhibitor Use and Survival in Urothelial Carcinoma Treated with Atezolizumab. Clinical Cancer Research. 2020;26:5487-93.
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Implementation and evaluation of a virtual pharmacy Objective Structured Clinical Examination (OSCE)

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Introduction. Objective Structured Clinical Examinations (OSCEs) have been used routinely in healthcare education programs. Traditionally, students undertake OSCEs as face-to-face interactions to assess competency in skills including problem solving, empathy and communication. Due to physical distancing restrictions during COVID-19, alternative methods of conducting OSCEs were required. Therefore, as part of our Pharmacy program, we implemented virtual OSCEs using the Zoom video conferencing system.

Aims. To evaluate pharmacy students and OSCE examiners' experiences of their first virtual OSCEs.

Methods. This study employed a mixed methods design. An online survey was administered in June 2020 to 196 second year pharmacy students after completion of their first virtual OSCE. All students completed the survey but students were required to consent to the use of their data for this study. Additionally, students were invited to provide contact details if they consent to a follow-up interview. In addition, all OSCE examiners (n=18) were invited to participate in an interview. Interviews were conducted via Zoom, transcribed verbatim and thematically analysed.

Results. A total of 87 % of students (n=170) consented to the use of their survey data. A further 10 students and 12 examiners were interviewed. The survey results showed that 33 % of students preferred the online virtual OSCE experience to face-to-face OSCE while 38% showed no preference to either methods. Only 20 % felt more anxious compared to the face-to-face OSCE while 12% agreed that the online virtual OSCE felt more challenging. From the interviews, both examiners and students identified non-verbal communication as a barrier during the OSCE. Students expressed challenges in displaying good non-verbal skills while examiners found difficulty evaluating these skills virtually. Positive aspects about virtual OSCEs were included flexibility, decreased levels of anxiety and the relevance with emerging practice such as telehealth.

Discussion. The need for remote online delivery of assessments saw innovative ways of undertaking OSCEs. The virtual OSCEs were an opportunity to mimic telehealth and current practice. This study found that while students and examiners embraced the virtual OSCE process, face-to-face OSCEs were still considered important and irreplaceable. Future opportunities for OSCEs to be delivered both face to face and virtually should be considered.

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Pharmacist-led intervention using a web-based tool to reduce high-risk medication use in older in-patients.

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Introduction. The Drug Burden Index (DBI) Calculator© is a web-based tool that measures exposure to anticholinergic and sedative medications. Increasing DBI score has been linked with negative health outcomes, including increasing frailty, falls and hospital readmission. As many older patients in hospital are prescribed large quantities of medications, tools such as the DBI Calculator©, may assist pharmacists in targeting deprescribing efforts.

Aims. To determine the feasibility and effect of integration of a web-based tool into pharmacist medication optimisation activities on high risk medication use in Canadian hospitals.

Methods. This was a prospective interventional implementation study. The intervention consisted of pharmacist-led medication review using The DBI Calculator© on admission and discharge with written reports to aid communication with physicians and patients/family. Those aged ≥70 years old admitted on one or more medications with anticholinergic or sedative properties were eligible to participate. The primary outcome was proportion who had decreased, increased or no change in DBI score during hospitalisation. Secondary outcomes included clinical outcomes (adverse drug events), feasibility (time taken by pharmacists) and fidelity (whether all elements of the intervention were conducted).

Results. Forty-five intervention participants across five sites were recruited; 40 participants had complete DBI data (mean age=82.5, 70% female). Twenty-six participants (65%) experienced a reduction in DBI score with 11 (27.5%) and 3 (7.5%) having no change and increase in score respectively. No adverse drug events related to the intervention were observed. Pharmacists took a mean of 13.2 minutes per participant to use The DBI Calculator© (range=5-20 minutes). Only 16/45 (35.6%) participants received all elements of the intervention. The most common element not delivered was communication with the patient/family before discharge.

Discussion. The intervention may be effective at reducing DBI scores in older adults during hospitalisation, however, significant feasibility issues were identified. Further work is required to determine the best way to integrate The DBI Calculator© into pharmacist workflow in hospital.

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Understanding the mechanisms behind the oral bioavailability enhancement of abiraterone acetate by silica-lipid hybrid formulations

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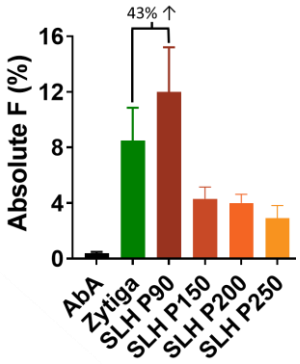
Introduction. Zytiga is a blockbuster oral treatment for prostate cancer, containing the active ingredient, abiraterone acetate (AbA). Despite its success, the Zytiga formulation is inefficient, possessing a <10% bioavailability and a 5 to 10-fold food effect. Patients take Zytiga in the fasted state at a large 1000 mg daily dose leading to poor compliance.

Aims. We aimed to develop an efficient oral lipid-based formulation for AbA using a supersaturated silica-lipid hybrid (SLH) approach to improve bioavailability and gain a mechanistic insight into how SLH digest and release AbA.



Methods. SLH were fabricated by dissolving AbA in lipid at 60 °C and subsequent encapsulation within nanoporous silica microparticles via mixing. Two lipids and four AbA saturation levels were investigated. Physicochemical characterisation, in vitro solubilisation and in vivo oral pharmacokinetic performance in fasted rats were examined.

Results. All SLH formulations achieved significantly greater in vitro AbA solubilisation during lipolysis than unformulated AbA (6 to 12-fold) and Zytiga (1.3 to 2.7-fold). In vivo, SLH formulations achieved 7 to 30-fold greater bioavailability than unformulated AbA, and SLHP90 achieved 1.43-fold greater bioavailability than Zytiga.

Discussion. AbA solubilisation was influenced by; (i) the AbA saturation level, where lower supersaturation levels maintained AbA in a non-crystalline form and increased the amount of co-dosed lipid, improving solubilisation, and (ii) the type of lipid, where the Capmul PG8 that loaded outside the silica particles and expelled fatty acids achieved greater solubilisation than Capmul MCM that loaded within the silica nanopores and retained digestion products. The amount of co-dosed lipid, rather than AbA crystallinity, played a major role in oral bioavailability enhancement. This data and mechanistic understanding of the SLH formulation, justifies further investigation into the development of a more efficient alternative oral formulation to Zytiga.

Schultz HB, et al. International Journal of Pharmaceutics **2020**, 119264.

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Evaluation of a pilot vancomycin therapeutic drug monitoring (TDM) service using an interrupted time series analysis

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Introduction. Bayesian forecasting software can provide individualised dose recommendations for patients.

Aim. To evaluate the ability of a pilot TDM Advisory Service to facilitate vancomycin therapeutic target attainment within a real-world clinical setting. The Service provided area under the concentration-time curve (AUC)-guided dose recommendations, using Bayesian forecasting software and clinical expertise, to prescribers at an Australian hospital.

Methods. A retrospective audit of intravenous vancomycin therapy (>48 hours) in adults (≥18 years) was undertaken over a 54-month period to evaluate attainment of established vancomycin pharmacokinetic/pharmacodynamic targets (AUC_{24}/MIC 400-600) pre- (36-months) and post-(18-months) implementation. Interrupted time series analysis was employed to evaluate monthly measures of the median proportion of therapy spent within the target range. Indices of time to target attainment were also assessed pre- and post-Service implementation.

Results. The final cohort comprised 1142 courses of vancomycin (816 patients); 835 courses (596 patients) and 307 courses (220 patients) administered pre- and post- Service, respectively. Tthe median proportion of time in the target range increased by 10.4% (95%CI: 1.2−19.6%, p=0.03) post-Service, and was sustained throughout the evaluation period. Post-Service target attainment at 48-72 hours after initiation of therapy was increased (7.8%, 95%CI: 1.3−14.3%, p=0.02) and there was a trend to increased target attainment at 24-48 hours after collection of the first TDM sample (5.9%, 95%CI:-1.1−12.8, p=0.10).

Discussion. The findings of this study provide evidence that a consultative Service can facilitate attainment of vancomycin therapeutic targets.

*Authors contributed equally to the work.

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Supporting and including our International students

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Introduction. In Australia, many of our international students encounter difficulties and challenges including English language barriers, cultural differences, loneliness, financial hardships and education system differences. Whilst information, administration services, societies and study support are available at the university level, the challenge is to provide regular campus-community based programs that foster a sense of belonging and well-being, most frequently cited factors for the academic success. Academic campus staff, given their educational perspective, present a unique way to foster connection with international students by providing support at a more intimate faculty level.

Aim. To develop and implement an inclusive campus community environment for international students at Monash's Faculty of Pharmacy and Pharmaceutical Sciences through an academic-led student engagement program.

Method. The program was designed to include a series of international student engagement activities, a quarterly newsletter and a central email as a unique port of call for academic support. The program focused on providing support through three key areas: 1) communication; 2) social and networking and; 3) wellbeing activities.

Results. A series of engagement and networking activities focused on skill development, social interaction and support were launched online. Activities included 'Studying virtually' and several 'Communication-focused' events that were driven by student interest. A 'Speed Networking' event where a personality test was used as a conversation starter was used to facilitate social interaction and networking. This event was particularly popular. Regular informal check-in sessions were held in the form of 'Pop-in Cuppa' sessions. A sense of community was further established by the launch of a quarterly newsletter featuring international students from the campus, upcoming events and Australian-themed competitions.

Discussion. Our program was designed to foster a sense of inclusive campus community with an impact on the well-being of international students. This program was also timely given the challenges and isolation brought on by the COVID pandemic. While engagement in activities varied, feedback was always extremely positive thereby validating that an academic-led student engagement program can create a welcoming environment in which international students feel connected, safe, and experience a sense of belonging.

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Promoting gender equity and diversity in the classroom

Tina Hinton. School of Medical Sciences (Pharmacology), The University of Sydney, Sydney, NSW, Australia.

What does it mean to promote gender equity and diversity in our classrooms? In this presentation I take a design approach to inclusion in our education, using a model for analysis of complex learning environments that considers physical and virtual design, task design and design for social interaction. These three design aspects converge to create the student experience and the learning behaviours that emerge from participation. Further, the language we use, the ways in which we encourage participation and how we reinforce our learners in real time are critical to a student's sense of belonging. I will demonstrate with examples and an historical analysis of curriculum components what we can all do to design for and promote equity and diversity in our classrooms.

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You wouldn't ask a goldfish to climb a tree! Neurodiversity and associated opportunities for inclusion and improved outcomes for all

Dr Arlene M Taylor, Ability Consultant, Integre Futures, Canberra, ACT, Australia

Neurodiverse students include those on the autism spectrum, diagnosed with attention deficit disorder/attention deficit hyperactivity disorder, and those with specific learning disabilities (including auditory processing disorder, dyslexia, and dyscalculia). Neurodiversity translates to different processing of information, and neurodiverse individuals can face (and pose) challenges during all stages of learning.

Join Arlene for a 'virtual simulation' of some challenges faced by neurodiverse students. Learn how to harness to the strengths and capability of these students through improved understanding of how neurodiversity impacts on different processes students and educators rely on in traditional learning environments. Discover how designing education tasks to be neuro-inclusive can enhance the learning process and overall outcomes for all students.

Come prepared to challenge personal ideas about what makes strong or effective learners: Consider where your current frameworks for teaching, assessing and engaging students can be enhanced with an inclusion focus.

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Strengthening Indigenous health workforces

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Introduction. In Australia, the ongoing process of settler colonialism seeks to eliminate Aboriginal and Torres Strait Islander people through various means. Health professions education has been complicit in this and in recent decades curriculum frameworks and accreditation requirements have sought to address this. However, few studies on these exist.

Aims. To employ critical Indigenous theory and action research to understand how an Indigenous health curriculum framework could be applied and improve equity in admissions of Indigenous students.

Methods. Three action research cycles were conducted of a discrete first year unit required for course accreditation. Student reaction (satisfaction and engagement) was collected via survey. Student learning was collated via self-perception survey (knowledge, attitude, confidence, commitment); MCQ (knowledge) and; content analysis of apply and analyse activities (skill). The teaching team met annually to reflect on findings and plan enhancements. Data were collected on admissions of Indigenous students over a five year period with annual reflection.

Discussion. Over the three years there was a pattern of improved student reaction and learning. The online delivery was scalable, overcame a barrier of educator skill and confidence to teach this area and provided critical consciousness building with students self-reflecting and planning how to act. In contrast, if teaching had occurred in small group oral discussions it would have been more difficult to ascertain teaching and learning occurring and undoubtably students would have received different messaging based on individual educator skill and confidence. Interestingly, learning gained from this unit matched that described as occurring from student placements in health settings with high numbers of Indigenous people. The discrete unit rapidly increased the level of Framework teaching and assessment in this undergraduate degree, higher than the average for Faculty disciplines attempting to integrate Indigenous health content. Notably the self-rated survey showed change for 23 items compared to five for a first-year integrated curriculum. Connecting this research to Faculty level committee led to widening success across the Faculty and improved sustainability of the practice. Equity in admissions of Indigenous students improved over the five-year period despite significant systematic challenges and obstacles.

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Dysregulated ALX/FPR2 ligand expression defines a novel molecular subtype of lung cancer

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Introduction. Globally, lung cancer is the leading cause of cancer related deaths. The tumour microenvironment in lung cancer is enriched with neutrophils, but their role in progression is poorly characterised. Chronic obstructive pulmonary disease (COPD) is also an inflammatory lung condition where patients are at increased risk of developing lung cancer. We have previously shown that Serum Amyloid A (SAA) contributes to neutrophilic inflammation in COPD by opposing the actions of specialised pro-resolving mediators (SPMs) that target the ALX/FPR2 receptor.

Methods. Archival fresh frozen and FFPE tumour tissue biospecimens (n= 20 control and n=40 adenocarcinoma) were obtained from the Victorian Cancer Biobank (VCB). A pre-clinical model of inducible lung adenocarcinoma harbouring the common kRas mutation (KrasG12D mice) was used to investigate the anti-tumorigenic actions of AT-Resolvin D1, a potent SPM that interacts with ALX/FPR2 and generated by the ALOX5 pathway.

Results. MPO-positive neutrophils were significantly increased within lung adenocarcinoma biopsies compared to control tissue. Whilst SAA expression levels were not significantly increased in adenocarcinoma biopsies, there was an accumulation of SAA-positive macrophages. In contrast, ALOX5 expression (key enzyme responsible for SPM production) was significantly reduced in adenocarcinoma biopsies. The SAA/ALOX5 ratio was highly elevated within tumour biopsies and correlated with increased neutrophilic inflammation. KrasG12D mice develop extensive lung tumours and treatment with AT-Resolvin D1 significantly reduced tumour area by approximately 50% and significantly reduced PCNA staining, a marker for cellular proliferation.

Conclusions. There is a subset of lung adenocarcinoma patients that express high levels of SAA relative to ALOX5 and this molecular imbalance is associated with an increase in tumour associated neutrophils. Resolvin D1 is a metabolite of the ALOX5 pathway and treating KrasG12D mice with AT-Resolvin D1 markedly reduced tumour progression.

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Lipoxins, a novel approach to treat diabetes-associated atherosclerosis

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The failure to resolve inflammatory responses results in chronic, insidious pathologies typified by vascular complications of diabetes such as accelerated atherosclerosis, diabetic kidney disease and compromised regeneration and repair. Our data indicate that LXs modulate vascular inflammation in murine models of diabetes. The development of diabetes-induced aortic plaques and inflammatory responses of aortic tissue including expression of *VCAM-1, MCP-1, IL-6* and *ILl-1ß* was significantly attenuated by both LXA4 and Benzo-LXA4 in diabetic ApoE-/- mice. Importantly, in mice with established atherosclerosis, treatment with LXs for a 6-week period, initiated 10 weeks after the induction of diabetes, led to a significant [p<0.01] reduction in aortic arch plaque development. LXs inhibited PDGF-stimulated vascular smooth muscle cells proliferation and transmigration and endothelial cell inflammation.

Treatment of human carotid plaque explants with LXs *ex vivo* attenuated secretion of proinflammatory cytokines including TNF-α and IL-1β. These data demonstrate that LXs can reverse established diabetic complications and support a therapeutic paradigm to promote the resolution of inflammation however, the costly synthesis and metabolic instability of LXs may limit their use in this context. We have generated novel imidazole-/oxazole-containing synthetic-LX-mimetics (sLXms) and will demonstrate their biological characteristics. These molecules evoke pro-resolving responses in in vivo and in vitro models of inflammation and fibrosis in the context of chronic inflammation.

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Advances in specialized pro-resolving mediator (SPM) G protein-coupled receptors

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Resolution of inflammation is regulated by specialised pro-resolving mediators (SPMs, such as resolvins and lipoxins) and their proposed cognate G protein-coupled receptors (GPCRs), including FPR2, BLT_1, $chemerin_1$, GPR32, GPR18 and GPR37. These receptors coordinate activity of peripheral blood mononuclear cells (PBMCs) and polymorphonuclear leukocytes (PMNs). However, the comparative pharmacology of SPMs and native immune cell expression profile of SPM-GPCRs are not well understood.

Therefore, we profiled (a) the expression levels of these SPM-GPCRs in PBMCs and PMNs of healthy human blood, and (ii) their responses to SPMs and surrogate ligands when stably expressed in HEK293 cells. Human $CD14^+$ PBMCs and $CD66b^+$ PMNs were isolated from whole blood utilising magnetic separation. FACS revealed almost ubiquitous expression of BLT_1 and GPR32 on the surface of PBMCs (89.5 ± 5.9% and 88.0 ± 7.7%; n=6-12) and PMNs (98.9 ± 0.9% and 87.5 ± 8.0%; n=6-11). FPR2 and $chemerin_1$ had a more restricted expression profile on PBMCs (29.3 ± 14.0% and 31.3 ± 18.7%; n=11-12) and PMNs (25.8 ± 14.8% and 14.5 ± 12.4%; n=11-12), whilst GPR18 was more abundantly expressed on PMNs (92.8 ± 3.3 %; n=6) versus PBMCs (34.3 ± 25.4%; n=6). No expression of GPR37 was detected.

However, with the notable exception of resolvin-E1 at BLT1, none of the previously reported SPM – SPM-GPCR ligand pairings were reproduced in multiple G protein-dependent or independent signalling assays in HEK293 cells in which canonical and synthetic ligands were robustly active (e.g. leukotriene-B4-stimulated BLT1 activation, WKYMVm-stimulated FPR2 activation). These data suggest that there may be more complex mechanisms by which SPMs interact with SPM-GPCRs in their native environment, if at all. Further studies in PMNs and PBMCs will be required to establish native SPM-GPCR pharmacology.

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Cardioprotective potential of resolving inflammation in the heart

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Inflammatory disorders such as diabetes and myocardial infarction are major causes of heart failure, which remains a key cause of death across the globe. The annexin-A1 (ANX-A1)/formyl peptide receptor (FPR) axis is integral to inflammation and its resolution. This presentation explores the potential for targeting this ANX-A1/FPR axis for cardioprotection, beyond their early anti-inflammatory effects to the prevention of late cardiac remodelling and dysfunction after myocardial inflammatory insults in mice *in vivo*. Choice of FPR ligand is key to the cardioprotective potential in the context of inflammatory disorders, whether small-molecule or peptide/lipid mediator based, and whether the ligand exhibits FPR-subtype selectivity and/or biased signalling downstream of FPR activation. Therapeutic targeting the ANX-A1/FPR axis may represent one approach to enhance the resolution of inflammation, and hence delay progression to heart failure, in both diabetic and ischaemic cardiomyopathies.

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Geographical and intra-facility variation in medicines use in Australian aged care facilities

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Optimising medicines management in Australian residential aged care facilities (RACFs) is a key focus of the Royal Commission into Aged Care Quality and Safety. Each year, 8% of older Australians access residential aged care services that are provided by >2,700 RACFs nationally. Older people living in RACFs are vulnerable to medicines-related harm due to high-risk medicines use, complex medication regimens, multimorbidity, frailty and frequent care transitions. In addition to resident characteristics, facility-level factors such as geographical location, ownership, facility volume, staffing, model of primary care service delivery and medication management processes can impact medicines use in RACFs. Understanding contributors to unwarranted variation in medicines use will help us to understand where we need to intervene to support quality use of medicines in RACFs, and inform quality improvement initiatives. This presentation will provide an overview of existing studies examining variation in medicines use and provision of collaborative medicines reviews across Australian RACFs.

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Unexplained variation in psychotropic use in aged care facilities: how does organisational culture contribute?

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Psychotropic prescribing, most commonly antipsychotics and benzodiazepines, in older residents living with dementia is highly reported and there is significant variation in the use of psychotropic medicines across residential aged care facilities (RACFs). This symposium will explain how organisational culture influences psychotropic prescribing decisions in RACFs using findings from three in-depth qualitative studies that involved internal and external RACF staff from diverse backgrounds and roles. The research was underpinned Schein's Theory of Organisational Culture that highlights what constitutes culture and captures the role of taken for granted beliefs that explain why members behave the way they do. Many aspects of culture that impede the appropriate use of psychotropic medicines include organisational support for multidisciplinary interventions (e.g. pharmacy-led medication review), limited communication by managers of residential care facilities to team members (both internal and external staff) about appropriate prescribing, and the involvement of residents and their representatives in prescribing decisions. An approach to psychotropic minimisation in RACFs is to evaluate the organisational culture. This can then be used by staff to identify specific aspects of the organisation that require improvement to reduce psychotropic prescribing or tailor multidisciplinary interventions to improve implementation.

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Medication Advisory Committees: A means to address unexplained variation in medication use

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Introduction. Multidisciplinary Medication Advisory Committees (MACs) are an Australian Government endorsed strategy to optimise medication safety and prevent medication-related harm in residential aged care facilities (RACFs). No previous research has explored how MACs can help optimise medication use through identifying and addressing unexplained variation in medication prescribing and administration.

Aims. The aims were to (1) investigate the current structure and function of MACs and (2) develop consensus recommendations for optimising MACs in RACFs.

Methods. Forty-four semi-structured interviews and focus groups were conducted with health professionals working across 27 Victorian RACFs. Data were thematically content analysed and presented to a 13-member multidisciplinary expert panel to develop consensus recommendations to optimise structure and functioning.

Results. There was consideration variation in the MAC membership and the mechanisms through which MACs sought to address quality use of medicines issues. The expert panel made 12 recommendations for improvement. Recommendations related to topics including audit and feedback using medication quality indicators (e.g. antipsychotic use, proton-pump inhibitor use, complex medication regimens), proactively identifying and responding to medication incidents, monitoring and evaluating high-risk medications, education and training of staff, and prioritising local and regional quality improvement initiatives.

Discussion. Opportunities exist to improve the structure and functioning of MACs to address unexplained variation in medication prescribing, administration and management. The 12 consensus recommendations for improvement provide a framework for proactively addressing emerging quality use of medicines issues.

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The Registry of Senior Australians (ROSA) outcome monitoring system: Quality and safety indicators for examining unwarranted care variation

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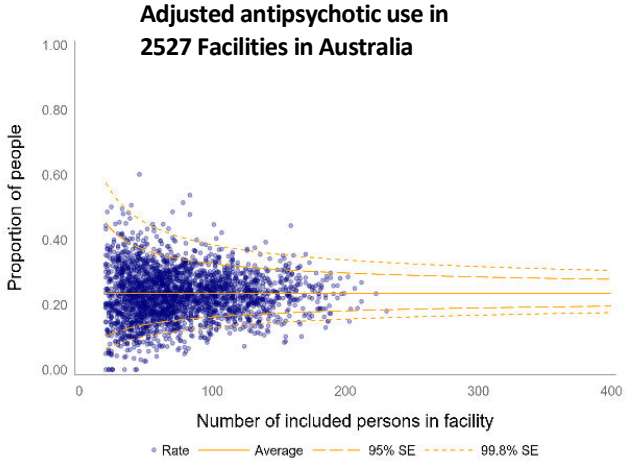
Introduction. An understanding of unwarranted variation, appropriateness, and effectiveness of care is currently lacking for the aged care sector in Australia.

Aims. To introduce the Registry of Senior Australians (ROSA) Outcome Monitoring System, which can monitor the quality and safety of care provided to individuals accessing residential aged care.

Methods. Twelve quality and safety indicators of care were developed based on the synthesis of existing literature and expert advisory input, and 2016 prevalence estimates and variation were examined using ROSA. Five indicators used national data sources (n=208,355) and 7 used SA state health records (n=18,956).



Results. Of the 5 indicators estimated nationally; antibiotic use (67.5%, 95% CI67.3-67.7%) had the highest prevalence, followed by high sedative load (48.1%, 95%CI 47.9-48.3%), chronic opioid use (26.8%, 95%CI 26.6-26.9%), antipsychotic use (23.5%, 95%CI 23.4-23.7%). Of the 7 indicators estimated in SA ED presentations (19.1%, 95%CI 18.3-20.0%) had the highest prevalence, followed by hospitalisation for falls (10.1%, 95%CI 9.7-10.4).

Discussion. Twelve quality and safety indicators were developed to monitor aged care quality provided to older Australians. These indicators rely on existing data within the aged care and health care sectors, therefore creating a pragmatic tool to examine quality and unwarranted care variation.

Inacio M, Lang C, Caughey GE et al (2020) Int J Qual Health Care. Jul 21; doi: 10.1093/intqhc/mzaa078.