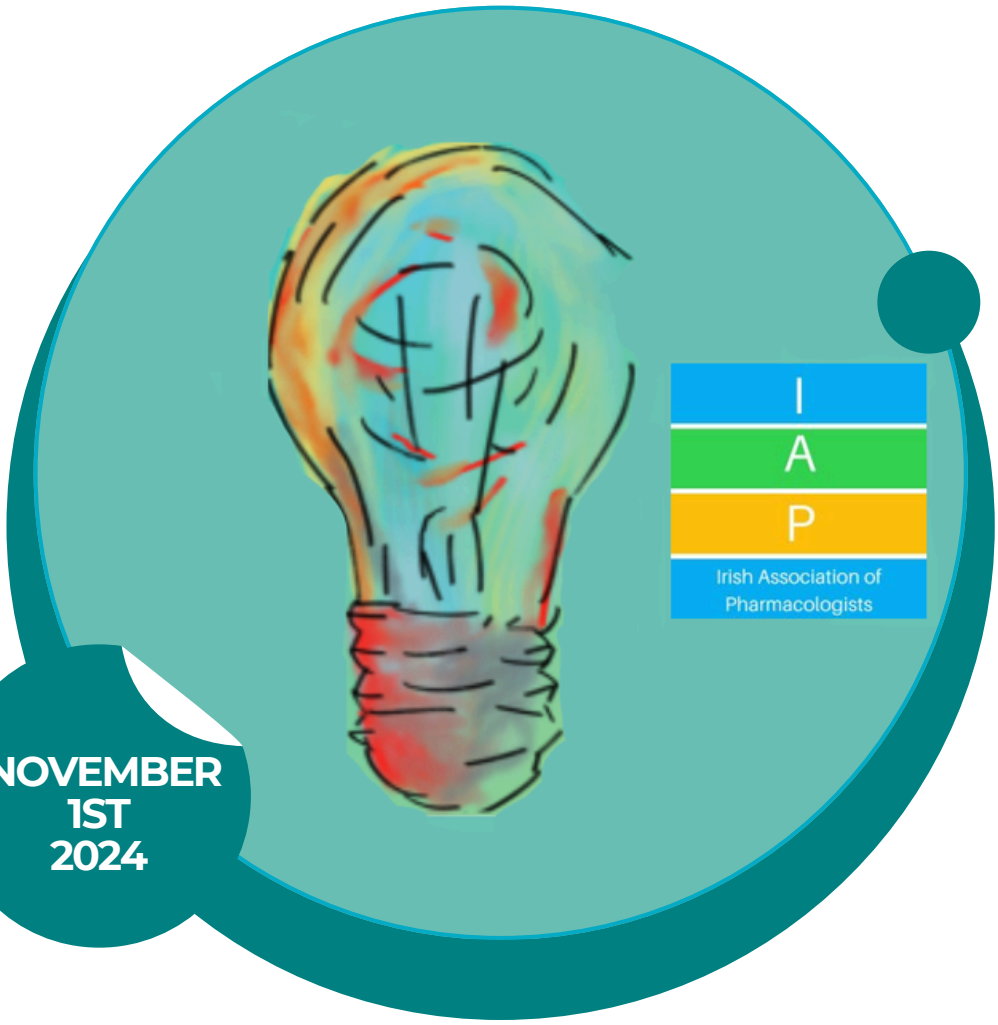
RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES



IRISH ASSOCIATION OF PHARMACOLOGISTS MEETING 2024

ABSTRACT BOOKLET

Uniting Science, Innovation, and Therapeutics

RCSI, St. Stephens Green, Dublin

Conference Schedule

Friday 1st November 2024	
09:30 – 10:15 am	Registration
10:15 – 10:20 am	IAP President's Welcome from Prof. Christian Waeber
SESSION 1 Clinical Pharmacology	
10:20 – 11:00 am **Keynote 1**	*Economic Considerations for Personalized Medicine: A Pharmacoeconomic Perspective* Prof. Michael Barry (Trinity College Dublin)
11:00 - 11:15 am	*Dissonance in the face of Alzheimer's disease breakthroughs: clinician and lay stakeholder acceptance, concerns and willingness to pay for emerging disease-modifying therapies* Prof. Iracema Leroi (TCD)
11:15 – 11:30 am	*Leveraging routinely collected electronic health record data to understand real-world treatment effects: trial emulation of the EMPA-REG outcome trial* Dr. David Ryan (UCL Hospital)
11:30 – 12:00 pm	Coffee Break and Moderated Posters
SESSION 2: Experimental Pharmacology	
12:00 – 12:40 pm **Keynote 2**	*Advances in Translational Therapeutics: Bridging the Gap from Laboratory to Patient* Prof. Clive Page (King's College London)
12:40 – 12:55 pm	*Screening the secretory profile of bone marrow fibroblasts post treatment identifies interleukin-10 (IL-10) as a therapeutic target to enhance myeloma killing* Dr. Graeme Sullivan (RCSI)
12:55 – 13:10 pm	*Chemical Adherence Testing in the Clinical Management of Hypertension: A Scoping Review* Dr. Louisse Rabbitt (UG)
13:10 – 14:00 pm	Lunch and Moderated Posters
14:00 – 14:45pm **John Feely Lecture**	*Clinical Pharmacology: A Hive of Activity* Prof. Philip Routledge (Cardiff University)
SESSION 3: Pharmacology Education	
14:45 – 15:25 pm **Keynote 3**	*From Dispensing to Prescribing: Expanding the Pharmacist's Role* Prof. Judith Strawbridge (RCSI University)
15:25 – 15:40 pm	*What do the student cohorts from University College Dublin truly think about the Prescribing Safety Assessment and how does this affect their performance?* Dr. Sami Termanini (UCD)
15:40 – 15:55 pm	*A Cross-Sectional Study of Recent Patterns of Psychotropic Medication Use in Children and Adolescents in Ireland* Ms. Rebecca Parkin (RCSI)
15:55 – 16:05 pm	Coffee Break
16:05 – 16:30 pm	Annual General Meeting
16:30 - 16:35 pm	Meeting Close and Prizes
16:35 - 17:00 pm **Round Table Meeting**	*How to Promote and Grow Pharmacology in Ireland* Prof. Weber, Prof. Routledge, Prof. Page, and Others
17:00 - Late	Networking in The Swan Bar

IRISH ASSOCIATION OF PHARMACOLOGISTS

The vision of the Irish Association of Pharmacologists (IAP) is to advance the understanding of pharmacology and its applications in health and disease through education, research, and collaboration. The IAP aims to promote excellence in pharmacological research and education in Ireland while fostering a vibrant community of pharmacologists, clinicians, and researchers.

By facilitating knowledge exchange, supporting professional development, and encouraging interdisciplinary collaboration, the IAP seeks to enhance the impact of pharmacology on public health and contribute to the development of innovative therapeutic solutions.

JOHN FEELY MEDAL

The Professor John Feely Medal commemorates the diverse and lasting contributions made by John Feely to the development of Pharmacology and Therapeutics in Ireland and internationally, in the course of a highly distinguished career both as a researcher and clinician.

The Professor John Feely medal is awarded by the Irish Association of Pharmacologist to an exceptional researcher who has made a highly significant contribution to basic or clinical pharmacology research on the island of Ireland.

RCSI

PBS

IAP 2024 HOST: SCHOOL OF PHARMACY AND BIOMOLECULAR SCIENCES

The School of Pharmacy and Biomolecular Sciences at RCSI is a leading institution in the fields of pharmacy, biomolecular science, and translational research. The school aims to achieve excellence in education, research, and community engagement, with a commitment to improving healthcare outcomes and patient safety. It strives to produce highly skilled graduates who are equipped to meet the challenges of modern healthcare systems and to contribute meaningfully to scientific advancements.

RCSI's School of Pharmacy and Biomolecular Sciences focuses on fostering innovation through interdisciplinary collaboration and research excellence, particularly in areas that address pressing health challenges such as Cancer, Infection, Immunity and Inflammation, Neurological and Psychiatric Disorders, Pharmaceutical Science and Biomaterials, Vascular Biology, Population Health and Health Services and Education Innovation. By integrating scientific research with clinical practice, the school envisions advancing the frontiers of knowledge in pharmacology, drug development, and biomolecular sciences, ultimately leading to improved therapeutic solutions and public health outcomes.

T-01

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Conference Theme: Other

Abstract Title: Dissonance in the face of Alzheimer's disease breakthroughs: clinician and lay stakeholder acceptance, concerns and willingness to pay for emerging disease-modifying therapies

Abstract Text

Background
Introducing new disease-modifying therapies (DMTs) for Alzheimer's disease demands a fundamental shift in diagnosis and care for most health systems around the world. Understanding the views of health professionals, potential patients, care partners and taxpayers is crucial for service planning and expectation management about these new therapies.
Aims
To investigate the public's and professionals' perspectives regarding (1) acceptability of new DMTs for Alzheimer's disease; (2) perceptions of risk/benefits; (3) the public's willingness to pay (WTP). Method Informed by the 'theoretical framework of acceptability', we conducted two online surveys with 1000 members of the general public and 77 health professionals in Ireland. Descriptive and multivariate regression analyses examined factors associated with DMT acceptance and WTP.
Results
Healthcare professionals had a higher acceptance (65%) than the general public (48%). Professionals were more concerned about potential brain bleeds (70%) and efficacy (68%), while the public focused on accessibility and costs. Younger participants (18–24 years) displayed a higher WTP. Education and insurance affected WTP decisions.
Conclusions
This study exposes complex attitudes toward emerging DMTs for Alzheimer's disease, challenging conventional wisdom in multiple dimensions. A surprising 25% of the public expressed aversion to these new treatments, despite society's deep-rooted fear of dementia in older age. Healthcare professionals displayed nuanced concerns, prioritising clinical effectiveness and potential brain complications. Intriguingly, younger, better-educated and privately insured individuals exhibited a greater WTP, foregrounding critical questions about healthcare equity. These multifaceted findings serve as a guidepost for healthcare strategists, policymakers and ethicists as we edge closer to integrating DMTs into Alzheimer's disease care.

Keywords: disease modifying therapies

T-02

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Conference Theme: Clinical Pharmacology

Abstract Title: Leveraging routinely collected electronic health record data to understand real-world treatment effects: trial emulation of the EMPA-REG outcome trial

Abstract Text

Introduction
Anti-diabetes medications, such as sodium-glucose co-transporter 2 inhibitors (SGLT2i), are increasingly prescribed for populations that were not represented in randomised controlled trials (RCTs). There is now an interest in using observational data to study real-world drug effects. Using a trial emulation framework, we began by emulating an important trial, EMPA-REG RCT, which was pivotal in establishing the cardioprotective benefits of empagliflozin in patients with cardiovascular disease and type 2 diabetes. We then extend the emulation to investigate effects in patients under-represented in the original trial.
Methods
We conducted a trial emulation using UK primary care data from the Health Improvement Network. Eligibility criteria were aligned with the original RCT. An active comparator design was employed, comparing initiators of empagliflozin to initiators of DPP-4 inhibitors from 01/01/2014 to 31/12/2022. The analysis followed an intention-to-treat approach, with all-cause mortality as the primary outcome. Confounding factors were adjusted for using adjusted and inverse-probability of treatment weighted (IPTW) Cox proportional hazard models, with missing data handled using multiple imputation. Hazard ratios estimated from the emulated trial were compared to those from EMPA-REG RCT using pre-defined agreement metrics. We then extended the emulation by removing all eligibility criteria and analysing all real-world recipients of empagliflozin to determine treatment effects.
Results
The emulated trial included 12,097 individuals. Among real-world users of empagliflozin, only 16.3% (n = 2,130) met the eligibility criteria for the EMPA-REG RCT. The emulated all-cause mortality hazard ratios agreed with published RCT figures. When the trial emulation was extended to a wider patient population, the population increased to 61,731 individuals, yet the treatment effects remained consistent.
Conclusions
This is the first population-based primary care emulation of the EMPA-REG RCT. Real-world populations who received empagliflozin were substantially different to those included in the RCT, but reassuringly, treatment effects were retained in real-world practice.

Keywords: Diabetes; Pharmacoepidemiology; Real-world evidence

T-03

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Conference Theme: Experimental Pharmacology

Abstract Title: Screening the secretory profile of bone marrow fibroblasts post treatment identifies interleukin-10 (IL-10) as a therapeutic target to enhance myeloma killing

Abstract Text

Despite major advances in the treatment of Multiple Myeloma (MM), it remains an incurable disease. Survival rates are improving but are still only marginally above 50% over five years. In MM, responses to treatment are not durable, resistance develops and the patient relapses. How such resistance emerges is poorly understood. We hypothesise that an influential aspect of treatment may be the secretory response of the tumour and associated stroma towards the therapeutic agent, altering the microenvironment and response to treatment. Here, we focus on the cell-death induced by two therapeutic agents: the proteasome inhibitor bortezomib (Velcade®), routinely used in upfront MM treatment. Additionally, we explore the BCL-2 antagonist ABT-199 (venetoclax), which has gained much attention in MM and is being investigated in ongoing clinical trials. Utilising MM tumour cell lines and patient samples we observed protection from the killing effects of bortezomib following co-culture with stromal bone-marrow fibroblast cell lines or patient-derived stroma. To our surprise, in the same systems, we found significantly enhanced venetoclax-induced cell death. Using various complementary techniques this dichotomous response was interrogated. BH3-profiling was used to assess mitochondrial priming and changes in anti-apoptotic dependence upon co-culture with stroma. Unbiased cytokine arrays were used to screen secretory factors that may be altering the sensitivity to drugs, with evidence of increased pro-inflammatory/pro-survival signalling factors upon drug treatment. Specifically, enhanced IL-6, IL-10 cytokine release and CCR2 receptor engagement in co-cultures was found, upon drug treatment. These observations are being explored further using mass-spectrometry secretome analyses in parallel with neutralisation strategies. Prospective results may identify improved therapeutic combinations for myeloma patients.

T-04

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Conference Theme: Clinical Pharmacology

Abstract Title:

Chemical Adherence Testing in the Clinical Management of Hypertension: A Scoping Review

Abstract Text

Introduction
Despite growing use, questions remain surrounding the utility, acceptability and feasibility of chemical adherence testing (CAT) as part of hypertension management in clinical practice.
This scoping review aimed to (i) identify and summarise studies using CAT in hypertension management, and (ii) describe and critically evaluate how CAT is currently being used in the clinical management of hypertension.
Methods
Peer-reviewed and published studies in English, reporting original research in any setting, with any study design, were included. Search concepts included hypertension, medication adherence, CAT, and their synonyms.
Searches were carried out using Ovid Medline, EMBASE, and PsycInfo (EBSCO), alongside manual searching of reference lists. Using Covidence software, we screened titles and abstracts, followed by full-text articles.
Results
Of the 618 studies identified, 48 were included. Studies were mostly published in high-income countries, focussed on treatment-resistant hypertension in secondary or specialist healthcare settings, and usually observational in design. 7 studies reported adherence analyses within clinical trials for hypertension therapies. Few studies measured the impact that performing CAT has on clinical outcomes for patients, such as BP control . The use of theoretical frameworks to guide reporting was rare, and there was considerable variation in key terminology and definitions, most notably in the definition of adherence. Some studies consider a participant adherent only if there is 100% concordance between their prescribed and detected AHDs, and consider all other results to represent nonadherence, while others differentiate between categories such as 'partial' and 'complete' nonadherence, though the thresholds for these categories vary. Such discrepancies are a significant barrier to the development of a cumulative evidence base.
Conclusions
The current body of evidence demonstrates considerable variability in the approach to implementing CAT for hypertension management in clinical practice, and a paucity of randomised controlled trials to evaluate its impact. Future research could (i) adopt a cohesive theoretical framework including clear operational definitions to standardise the approach to this important topic; (ii) further explore the impact of CAT on clinical outcomes using RCTs.

Keywords: Hypertension, Medication Adherence, Chemical Adherence Testing

T-05

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Conference Theme: Pharmacy/Pharmacology Education

Abstract Title: What do the student cohorts from University College Dublin truly think about the Prescribing Safety Assessment and how does this affect their performance?

Abstract Text

Introduction
The Prescribing Safety Assessment (PSA) is a validated exam run by the British Pharmacology Society and the Medical Schools Council (UK). It is designed to assess preparedness to prescribe. In the UCD School of Medicine, we have offered the PSA to all final year medical students since its inception. Since 2022, we have also delivered the PSA to doctors in our intern network without previous PSA certification.
Objectives
This study examined PSA performance predictors, as well as attitudes to the PSA and prescribing safety among different student cohorts sitting the exam.
Methods
Our analysis used performance and feedback data from five PSA sittings (2019-2024). Resit and remote sittings (2021) were excluded. Using a ranking method, PSA performance was analysed by degree programme (direct vs. graduate entry medicine), candidate nationality, and final degree GPA score. Feedback scores and comments from undergraduates and interns were compared for the period 2023-2024. A detailed survey of attitudes to prescribing and the PSA was conducted for the 2024 intern cohort (n=75).
Results
Despite varied pre-clinical pharmacology exposure, direct-entry and graduate-entry PSA rankings were not significantly different. UK and Irish candidates outperformed other nationalities, but among the whole class-group, final degree GPA and PSA ranking did not correlate. Both final medical students and interns agreed that the PSA should be passed before starting internship. PSA exam length/timing and lack of practice material were candidate complaints. Those interns who had not passed the PSA in medical school reported that 'learning on the job' improved their prescribing abilities more than focused education.
Conclusions
Putting in place a mandatory requirement for both undergraduate students and interns to sit the PSA improves engagement and raises awareness of prescribing safety.

Keywords: Prescribing education; Medication safety

T-06

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Conference Theme: Clinical Pharmacology

Abstract Title:

A cross-sectional study of recent patterns of psychotropic medication use in children and adolescents in Ireland

Abstract Text

Aim: There has been a global rise in prescribing of psychotropic medications. Variations in patterns of use, according to age group, gender and drug class type, have also been reported. This study aimed to analyse patterns of psychotropic medication use in Ireland according to age group, gender and drug class type, to determine if variations exist, and identify specific nuances to be addressed in future research.

Methods: A retrospective, repeated, cross-sectional study of the Irish pharmacy claims database (community setting dispensing data) was conducted. Yearly prevalence of children/adolescents receiving dispensed psychotropic medications was analysed from January 2017 to December 2021, across years, age groups (5-15, 5-11 and 12-15 years), gender and drug class type. All available data were used. Yearly prevalence was the mean number of patients receiving medication per month per 1000 eligible population during a given year. Negative binomial regression was used to examine association of year, age group and gender on prevalence.

Results: In the 12-15 years group, prevalence for all selected psychotropic medications in 2021 in males was almost twice that in females (19.92/1000 vs 10.62/1000). In the 5-11 years group, prevalence was three times higher in males than females (7.56/1000 vs 2.49/1000). Overall, there was a higher rate of increase in females and higher overall usage in older children. Sertraline has overtaken fluoxetine as the most commonly dispensed antidepressant and quetiapine has become the third most commonly dispensed antipsychotic.

Conclusion: This study found variations in psychotropic medication use in children/adolescents, depending on age, gender and drug class type. Further research is needed to determine whether variations have resulted in treatment disparities for certain cohorts.

Keywords: psychotropic medication, children, patterns

P-01

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Conference Theme: Experimental Pharmacology

Abstract Title: β-amyloid's neurotoxic mechanisms as defined by in vitro microelectrode arrays

Abstract Text

Alzheimer's disease is characterised by the aggregation of β-amyloid, a pathological feature believed to drive the neuronal loss and cognitive decline commonly seen in the disease. Given the growing prevalence of this progressive neurodegenerative disease, understanding the exact mechanisms underlying this process has become a top priority. Microelectrode arrays are commonly used for chronic, non-invasive recording of both spontaneous and evoked neuronal activity from a variety of diverse in vitro disease models and to evaluate therapeutic or toxic compounds. To date, microelectrode arrays have been used to investigate β-amyloids' toxic effects, β-amyloids role in specific pathological features and to assess pharmacological approaches to treat Alzheimer's disease. The versatility of microelectrode arrays means these studies use a variety of methods and investigate different disease models, brain regions and potential therapeutic compounds. We conducted a systematic overview of these studies, highlighting the main outcomes and disparities based on the status of the current literature and recent findings from our laboratory. Despite methodological differences, the current literature and our results indicate that β-amyloid has an inhibitory effect on synaptic plasticity and induces network connectivity disruptions. β-amyloid's effect on spontaneous neuronal activity appears more complex. Overall, the literature and our findings corroborate the theory that β-amyloid induces neurotoxicity, having a progressive deleterious effect on neuronal signalling and plasticity. These studies also confirm that microelectrode arrays are valuable tools for investigating β-amyloid pathology from a functional perspective, helping to bridge the gap between cellular and network pathology and disease symptoms; while also being a useful method for high-throughput evaluation of potential therapeutics for Alzheimer's disease.

Keywords: Alzheimer's disease, Neurodegenerative disease, Microelectrode array

P-02

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Conference Theme: Experimental Pharmacology

Abstract Title: Evaluation of preclinical antipsychotic models used to support first-in-human clinical trials

Abstract Text

Introduction: Schizophrenia is a heterogeneous psychiatric disorder inadequately treated with current antipsychotic drugs due to insufficient effectiveness and/or side effects, representing a need for novel antipsychotics (Jauhar S. et al., 2022, Lancet 399: 473). Preclinical testing plays a pivotal role in evaluating novel antipsychotics, and models have been developed to mimic certain disease features (Spark DL et al. 2022, Transl Psychiatry 12:147.). Thus, the aim of this study was to appraise the models used to assess antipsychotic efficacy in new drug applications (NDAs) submitted to the US Food and Drug Administration (FDA) for approval, and those used for novel investigational agents in support first-in-human clinical trials.

Method: We identified preclinical (i.e. rodent) tests used to evaluate the efficacy of marketed antipsychotics from the past 30 years by consulting the NDAs that were reviewed by the Centre for Drug Evaluation and Research (CDER) of FDA. Likewise, we investigated novel drugs that have undergone premarketing clinical development by consultation of the Clinical Trials repository, from which comparable preclinical data were obtained from the published literature.

Results: We found that all marketed drugs primarily target dopaminergic and/or serotonergic receptors, and preclinical rodent models used reflect this by employing dopaminergic and serotonergic agonist challenges. Additionally, we identified investigational drugs that have at least reached phase 2/3 clinical trials and have various mechanisms of action, in which tests have focused on dopaminergic and serotonergic agonist challenges, with additional use of glutamatergic receptor challenge. However, many of them have failed in subsequent clinical phases of development due to lack of efficacy.

Conclusions: Preclinical evaluation of antipsychotic activity has to date focused on a limited number of tests that challenge dopaminergic, serotonergic and glutamatergic receptors. Greater diversity in the preclinical models may improve the detection rate of novel antipsychotics that are more likely to be clinically effective.

Keywords: Schizophrenia, antipsychotic drug, animal model

P-03

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Conference Theme: Experimental Pharmacology

Abstract Title:

A closed-loop antihypertensive drug-delivery system for management of hypertension and blood pressure variability

Abstract Text

Hypertension remains a leading cause of cardiovascular morbidity and mortality globally, with blood pressure (BP) variability emerging as a contributor to cardiovascular risk.(1,2) The CLADDAGH (Closed-Loop Antihypertensive Drug-Delivery Algorithm in Hypertension) project aims to develop and test an implantable closed-loop antihypertensive drug-delivery system to manage hypertension and reduce BP variability, serving as a proof of concept for precision medicine in BP management.

Methods:

A two-phase experimental approach will be performed using stroke-prone spontaneously hypertensive rats. Phase 1 involves administering incremental doses of Esmolol hydrochloride via a subcutaneous pump, following a fixed oral dose of Amlodipine, to establish dose-response curves. Phase 2 will utilise proportional integral derivative (PID) algorithms derived from Phase 1 data to control the timing and dose of Esmolol release, optimising BP control and minimising variability (coefficient of variation), dependent on real-time BP and HR data.

Results:

Early results will facilitate development of PID algorithms that adjust Esmolol dosages based on real-time monitoring of BP and HR. These algorithms will initially be validated on an already existing BP dataset. The closed-loop system will be composed of: i) radiotelemetry measurement of BP and HR, that will communicate wirelessly with ii) a controller that contains the sets of algorithms, that will determine the timing and release of Esmolol via the iii) implantable, subcutaneous pump. A custom application will allow for review of live BP, HR and coefficient of variation values during the closed-loop system administration to monitor system responsiveness. Phase 2 of the study will test the closed-loop system in a stroke-prone spontaneously hypertensive rat model.

Conclusions:

The initial stages of the CLADDAGH project are focused on establishing a robust foundation for a closed-loop antihypertensive drug delivery system. Preliminary findings on algorithm development and real-time analysis of cardiovascular data will be presented, anticipating a proof-of-concept for managing hypertension and BP variability.

Keywords: Hypertension, Closed-Loop, Blood pressure variability

P-04

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Conference Theme: Experimental Pharmacology

Abstract Title: Characterisation of cognition-, anxiety- and depression-related behaviour and the endocannabinoid system in a rat incisional wound model

Abstract Text

Anxiety and depression are common comorbidities in individuals with chronic wounds. The endocannabinoid system (ECS) has a role in the modulation of cognition and negative affect. This study characterised cognition-, anxiety- and depression-related behaviour in the hairy skin back incision (BI) wound model in rats of both sexes and investigated alterations in the ECS.

Male and female Sprague-Dawley rats (150-200g on arrival, n=9/group) underwent BI or sham surgery. Anxiety-related behaviour was assessed using the light-dark box, elevated plus maze and open field tests between post-surgery days (PSDs) 5 and 30. The sucrose preference test assessed depression-related behaviour on PSDs 17-18. Cognition-related behaviour was assessed using the novel object recognition test on PSD 31. Rats were euthanised on PSD 35, and brains were gross-dissected and snap-frozen. Quantification of endocannabinoids (2-AG and AEA) and N-acylethanolamines (PEA and OEA) was carried out by LC-MS/MS. RT-qPCR assessed endocannabinoid-related gene expression in discrete brain regions.

There was no effect of BI on cognition-, anxiety- or depression-related behaviour. Female sham and BI rats spent more time in the open arms of the elevated plus maze and had higher locomotor activity in the open field than their male counterparts. Post-mortem analysis revealed higher striatal levels of 2-AG in females compared to males, which was positively correlated with locomotor activity. Female BI rats had increased levels of mRNA encoding mgll (the gene encoding monoacylglycerol lipase which catabolises 2-AG) in the striatum vs female shams.

These results indicate sex differences in anxiety-related behaviour, locomotor activity, and the ECS. Further work is required to determine the implications of increased striatal expression of mRNA encoding mgll post-incision in female rats.

Acknowledgements: Funding was provided by the Irish Research Council Postgraduate Scholarship, Science Foundation Ireland and B. Braun Hospicare and is co-funded under the European Regional Development Fund under Grant Number 13/RC/2073-P2.

Keywords: Wound; Anxiety; Endocannabinoid System

P-05

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Conference Theme: Experimental Pharmacology

Abstract Title: *Discovering Novel Synergistic Drug Combinations for Targeted Cancer Cell Therapy with a Multiplex Screening Method*

Abstract Text

Introduction: High-grade serous ovarian cancers (HGSOCs) are recalcitrant and difficult to treat cancers. Despite ongoing efforts to develop new therapies, patients, both existing and newly diagnosed, still confront relapse and poor outcomes. High-throughput screening of existing drugs offers promise in identifying novel drug responses and biomarkers for tailored treatment.

Methods: The FDA-approved drugs and their pairwise combinations were screened in 2D cultures of 5 HGSOC cell lines using cell toxicity or viability assays. Drug synergy was analysed using the Bliss independence, the multidimensional and the Loewe additivity models. A further high throughput screening approach was optimised to test drug responses in 3D spheroid cultures derived from the HGSOC cell lines or the ascitic fluid of ovarian cancer (OC) patients.

Results: The hierarchical clustering of 112 drugs' responses successfully differentiated chemo-sensitive from chemo-resistant cell lines. The drug combination screens revealed synergy between anti-cancer drugs targeting DNA repair and the cell cycle pathways in chemotherapy-sensitive cell lines, while combinations of inhibitors of PI3K and the mevalonate pathways exhibited synergistic cytotoxicity in chemo-resistant cell lines. Preliminary 3D drug screening using CellTOX Green and PrestoBlue assays enabled simultaneous detection of cell death and viability for 100 drugs.

Conclusion: Our ongoing research focuses on elucidating molecular features of novel drug responses in HGSOC and developing a rapid protocol for culturing cancer spheroids from OC patient ascitic fluid. High throughput drug screening approaches, if applied to patient-derived samples, could uncover an actionable cytotoxic drug response profile of a patient's disease.

Keywords: Ovarian cancer; Drug screening; Combination therapy

P-06

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Conference Theme: Experimental Pharmacology

Abstract Title: *Insights into the biological effect of targeting CDK12 in advanced ER+ breast cancer*

Abstract Text

A better understanding of breast cancer progression to metastasis is critical for identifying new therapeutic targets. Preliminary data from our lab described the role of CDK12 in regulating the pro-tumorigenic signalling in advanced ER+ breast cancer, and showed evidence of CDK12 modulating ER and MED1 chromatin accessibility. In this work we extend and validate these findings in novel cellular models and explored the biological outcomes of targeting CDK12 in advanced ER+ breast cancer.

By immunofluorescence, CDK12 was found to be co-expressed with ER and MED1 proteins in the nuclei of advanced ER+ breast cancer cells. By co-immunoprecipitation we found that ER/MED1 interaction was disrupted when CDK12 was inhibited, providing a mechanistic explanation for CDK12 regulating estrogen signalling. We then used a small molecule inhibitor (CT7116) to target CDK12 in our cells, and found that besides ER and MED1, CT7116 reduced the expression of CDK12 partners CDK13 and CCNK, as well as total and activated form of RNA Pol II. Previous RNA-seq investigations revealed that besides ER signalling, CDK12 regulated DNA-repair, apoptosis and cell cycle progression. Indeed, pharmacological targeting of CDK12 with CT7116 led to a loss of RAD51 and gain of γH2AX expression, indicative of DNA damage. Likewise, the treatment resulted in increased expression of the apoptotic marker cPARP and CDKN1A, a cyclin-dependent kinase inhibitor. Finally, we explored the use of CT7116 in combination with standard-of-care therapies for advanced ER+ breast cancer (fulvestrant and ribociclib) for which our cell models were resistant to. By drug synergistic experiments, we ratified the sensitivity of our models to the use of CT7116, and defined the combo treatment to be likely additive.

Altogether, our data defined the functional effects of targeting CDK12 in advanced ER+ breast cancer and encourage further studies on CDK12 transcriptional mode of action in endocrine resistant and metastatic breast cancer.

Keywords: Breast Cancer, CDK12, Drug synergy

P-07

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Conference Theme: Experimental Pharmacology

Abstract Title: Design of a prototype delivery system to improve oral bioavailability of poorly permeable peptides

Abstract Text

Therapeutic peptides are a drug class with excellent safety, efficacy, and tolerability. However, their widespread use is limited by low oral bioavailability due to pre-systemic degradation and low intestinal permeation attributed to their high molecular weight and hydrophilic properties.

The primary aim of this study was to transiently increase the lipophilicity of a model hydrophilic peptide to facilitate passive intestinal permeation and ultimately increase oral bioavailability. The lipophilic peptide, prepared by hydrophobic ion pairing (HIP), was solubilised in a self-emulsified drug delivery system (SEDDS) and combined with an intestinal permeation enhancer (PE) to maximise intestinal permeation, forming the novel oral drug delivery system (DDS).

An in vitro screen of PE candidates in Caco-2 monolayers identified trehalose 6-laurate (TE12) as the most effective PE, demonstrating a 13-fold greater Papp of FD4 than sodium caprate. This result was confirmed on rat colonic mucosae, where an 8-fold increase in Papp coupled with moderate reductions in % TEER was observed, while tissue functionality was preserved, thus justifying its selection for inclusion in the DDS. Following screening of amphiphilic counterions to perform HIP with the model peptide leuprolide, sodium docusate was selected, resulting in a 3.2-fold increase in octanol partitioning. A SEDDS was developed allowing successful loading of leuprolide docusate. Characterisation of the dispersed SEDDS revealed formation of a nanoemulsion that offered modest protection of leuprolide by HIP and SEDDS against the action of trypsin.

The complete DDS caused 4-fold and 7-fold increases in the Papp of leuprolide across Caco-2 monolayers and rat colonic mucosae, respectively. Furthermore, no loss of colonic tissue viability was observed upon exposure to the DDS or its components, providing preliminary toxicology data for the DDS.

This study provides evidence that incorporating lipophilic peptides into SEDDS and co-delivery with a permeation enhancer can increase peptide permeation.

Keywords: Oral peptide delivery, SEDDS, Intestinal permeation enhancer.

P-08

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Conference Theme: Experimental Pharmacology

Abstract Title: Reversal of Epigenetic Dysregulation in Breast Cancer Brain Metastasis via HDAC1/2 Inhibition

Abstract Text

Background

Breast cancer metastasizing to the brain poses significant clinical challenges due to its severe prognosis and limited treatment options. Investigating the molecular mechanisms behind breast cancer brain metastasis (BCBM) is crucial for the development of targeted therapies. The adaptability of cancer cells in the brain, likely driven by epigenetic modifications, highlights the potential for targeted epigenetic interventions.

Materials and Methods

We analysed a clinically characterized cohort of primary breast tumours and brain metastases using RNA sequencing for pathway enrichment. This was complemented by integrating Chromatin-Immunoprecipitation (ChIP)-seq data with brain metastasis transcriptomes and conducting pharmacological screening across various cell line models to pinpoint vulnerabilities.

Results

Our research identified a pivotal role for the co-REST transcriptional network and its associated histone deacetylases (HDACs) in managing brain metastasis. Elevated REST levels were linked to poorer outcomes in brain metastasis cases. Pharmacological assessments pinpointed to the HDAC pathway as a viable therapeutic target, corroborated by in vitro and ex vivo validations using patient-derived organoids. Crucially, targeting HDAC1/2 with quisinostat effectively hindered metastatic progression–a notable improvement over outcomes from singular HDAC targeting, as seen in glioblastoma studies. Further mechanistic investigations highlighted the involvement of the HER/AKT/mTOR and TGF-β pathways in BCBM.

Conclusions

Our findings establish the REST/HDAC axis as a key promoter of BCBM. Quisinostat, by specifically inhibiting HDAC1/HDAC2, demonstrated significant effectiveness, indicating its potential as a management strategy for brain metastases. This approach underscores the promise of HDAC inhibitors with enhanced selectivity and brain penetration as emerging tools in neuro-oncology.

Keywords: Breast cancer brain metastasis, Epigenetics, CoREST complex

P-09

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Conference Theme: Experimental Pharmacology

Abstract Title: Critical role of immunophilin FKBPL in the pancreas: An Islet Perspective

Abstract Text

FK506-binding protein-like (FKBPL), a member of the immunophilins family, is well recognized for its anti-angiogenic and anti-stemness properties in cancer therapy. However, recently emerging evidence has implicated FKBPL in key pathways associated with obesity and Type 2 Diabetes (2DM).The current study investigates the role of FKBPL in islet function and development, providing novel insights into its critical involvement in islet morphology, cell identity, and the regulation of pancreatic beta-cell function.

P-10

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Conference Theme: Experimental Pharmacology

Abstract Title: An investigation of the effects of Aquamin treatment on global gene expression in primary murine macrophages

Abstract Text

Introduction: Aquamin (Aq) is a multi-mineral supplement derived from the red algae Lithothamnion glaciale. Clinical studies have demonstrated the health benefits of Aq in the context of osteoarthritis. Anti-inflammatory properties of aquamin have been observed in vitro, indicating its importance as a functional food to regulate immune health. Many chronic disorders including cardiovascular disease have their pathology rooted in inflammation and immune cell dysfunction. This project will characterise the significance of Aq in modulating immune pathways associated with driving atherogenesis.

Methods: Primary murine bone marrow macrophages (BMDMs) were subjected to the following treatments: LPS (100 ng/ml), Aq (2 mg/ml) and LPS+Aq, including an untreated control group. The mRNA from these cells was isolated following incubation with the above compounds this treatment and next generation sequencing analysis performed to quantify changes in gene expression. Human peripheral blood mononuclear cells (PBMCs) were isolated from whole blood donations and stimulated with LPS and Aq as above for 6h and 24h. RT-PCR and ELISA were used to investigate the effects of Aq on expression of pro-inflammatory cytokine changes identified in the sequencing analysis above.

Preliminary Results: Functional pathway analysis such as KEGG and GO revealed a profile of differentially expressed genes (DEGs) that were altered in LPS-treated macrophages vs LPS+Aq. For example, many genes from the cytokine-cytokine receptor interaction, IL-17 signalling, and inflammatory bowel disease (IBD) pathways are downregulated in LPS+Aq vs LPS treatment group. Aquamin also modulates production of TNF alpha in human PBMCs, on both gene and protein level, as seen in in vitro cell assays.

Discussion and further analyses: Ongoing analyses will further characterise the effects of Aq on vascular cell migration and monocyte invasion using in vitro models. Additionally, the expression of cell adhesion and inflammatory markers associated with atherosclerosis pathology will be assessed. Ultimately, these results will improve current understanding of the mechanisms by which intake of Aq may improve the pathology of atherosclerosis.

Keywords: Inflammation; atherosclerosis, immune function

P-11

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Conference Theme: Experimental Pharmacology

Abstract Title: p38delta/MAPK13 as a biomarker for epigenetic drug chemosensitisation to cytotoxic drugs in oesophageal squamous cell carcinoma.

Abstract Text

Introduction: Oesophageal cancer is a leading cause of cancer-related deaths worldwide with a 13% incidence in Ireland (1). Current treatment strategies with conventional cytotoxic drugs, 5-fluorouracil/oxaliplatin are ineffective (5-year survival rate remains <20%) (2). Hence, there is an unmet critical need to develop new effective therapies. Oesophageal cancer is characterised by genetic and epigenetic changes, the latter being pharmacologically reversible. We showed that epigenetic drugs (DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi)) are selectively cytotoxic to oesophageal squamous cell carcinoma (OESCC) (3). Using methylation-specific and bisulfite sequencing PCR, we identified MAPK13 promoter hypermethylation in OESCC, leading to gene silencing (4). Furthermore, we showed that the p38δ MAPK status is an indicator of conventional cytotoxic drug therapy sensitivity (5).

Methods: Cell proliferation, viability and survival of OESCC (KE-8) p38δ+/- cells (2D models) were measured using the Presto Blue resazurin assay (short-term) and clonogenic growth (long-term). Cells were pretreated with the repurposed epigenetic drugs, disulfiram(DSF) (DNMTi), valproic acid(VPA) (HDACi) and metformin(MET) (miRNA) followed by 5-FU/oxaliplatin. 3D KE-8 p38δ+/- spheroids were used to mimic the in vivo environment.

Results: Epigenetic drug IC50 values were lower in KE-8 p38δ+ cells vs p38δ- cells; DSF; 13.8μM/27.2μM; VPA 1.1mM/7.4mM; MET 7.5mM/29.2mM. DSF (20 μM) sensitised KE-8 p38δ+ cells to 5-FU (10 μM) and oxaliplatin (0.5 μM) resulting in >90% cell death (50% in p38δ- cells). Long-term effects of DSF (20 μM) pretreatment resulted in 0% KE-8 p38δ+ colony development (KE-8 p38δ- cells demonstrated >75% colony development). DSF chemosensitisation was unique in KE-8 p38δ+ cells but not observed with either VPA or MET.

Discussion: p38δ MAPK may be a biomarker for DNMTi (but not HDACi and miRNA) chemosensitisation in OESCC. Further research using additional DNMTi is required to determine the usefulness.

Keywords: Oesophageal squamous cell carcinoma, p38delta MAPK, epigenetics

P-12

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Conference Theme: Experimental Pharmacology

Abstract Title: Finely modulating the human macrophage phenotype: A rationale for a pro-resolving approach combined with gold-standard therapy in atherosclerosis

Abstract Text

Atherosclerosis is a progressive, multi-factorial disease characterised by the build-up of plaque, underpinned by chronic inflammation. Our focus lies along the monocyte-macrophage-foam cell axis, characterising disease progression, by worsening related imbalanced lipid metabolism and low-grade inflammation.

We firstly set up a relevant in vitro model of early atherogenesis before intervening with pro-resolving agents.

THP-1 monocytes are transformed into various macrophage phenotypes across 6 days in response to a combination of differentiating (PMA, M-CSF, GM-CSF) and polarising (IL-1B, IL-4, IL-10, TRAIL) stimuli, before transcriptomic analysis of cell markers, cytokines, scavenger receptors, and TRAIL pathway effectors.

After exposing pro-inflammatory macrophages to dil/ox-LDL for 4hrs, foam cell formation was monitored by measuring lipid uptake (via Sartorius-Incucyte and by transcriptomic analysis of influx/efflux proteins.

Various stimulus-dependent macrophage profiles were observed by RNAseq/RT-PCR, suggesting an anti-inflammatory phenotype M-CSF/IL-4-driven, as well as a resolving subtype GM-CSF/TRAIL-driven. Moreover, TNF-stimulated-macrophages showed significant uptake/retention of lipids vs vehicle ($p<0.0001$).

An interventional study was performed using 100nM LXA4 and its mimetics to monitor their effect on gene/protein expression and on the migratory properties of monocytes and M1 macrophages.

In particular, 25ng/ml Monocyte Chemoattractant Protein-1 (MCP-1) or Plaque Conditioned Media (P.C.M.) (human atherosclerotic specimens cultured 24hrs with 5ng/ml TNF) served as chemoattractants for monocyte and M1-macrophage migration, revealing an enhanced trend of monocyte migration towards MCP-1, whilst M1-macrophages migrated towards P.C.M. 2-3X more ($p<0.0001$).

Overall, we have established a relevant model of early atherogenesis to exploit efficacy and potency of resolving agents alone and in combination with gold-standard lipid lowering drugs.

Keywords: Atherosclerosis, Macrophage plasticity, Specialised pro-resolving mediators

P-13

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Conference Theme: Experimental Pharmacology

Abstract Title: An in vitro Study of the Crosstalk Between the Androgen Receptor and SRF in Castrate Resistant Prostate Cancer

Abstract Text

Cell proliferation and migration in prostate cancer (PCa) is driven by androgen signalling. Thus, current treatments for PCa involve hormone therapies, such as targeting the Androgen Receptor (AR) with drugs like Enzalutamide. While these treatments are initially effective, many patients develop resistance leading to terminal prognoses. Serum response factor (SRF) has been identified as a key co-regulator of AR and potential target to combat this resistance. Previous research in the lab identified common co-regulators implicated in the AR/SRF crosstalk via mass spectrometry followed by co-immunoprecipitation. The aim of this study was to investigate the effects of pharmacological inhibition of the common co-regulators, singly and in combination, as potential treatment avenues.

Two PCa cell lines of different origin, C4 and 22Rv1, were selected due to their expression of characteristics of treatment resistance. We performed cell viability MTT assays using inhibitors that were proven effective in other PCa cell lines: CCG-1423 (SRF inhibitor), Lestaurtanib (SRF inhibitor), EPI-7170 (AR-V7 inhibitor), Ipatasertib (AKT inhibitor) and VER-155008 (HSP70 inhibitor). The results showed that these inhibitors decreased cell viability in both cell lines.

Furthermore, we performed drug combination assays based upon previous cell proliferation data and analysed their combination index using the CompuSyn software. These results showed strong synergistic effects between the combinations, including at concentrations lower than the IC50 values of single treatments, in both cell lines.

In conclusion, drug combinations showed encouraging synergy in PCa cell lines. This may provide a promising avenue for novel therapeutic targets in treatment resistant PCa.

Keywords: Prostate Cancer, Drug Combinations

P-14

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Conference Theme: Experimental Pharmacology

Abstract Title: Development of zebrafish xenograft models for oncology drug discovery.

Abstract Text

Treatment avenues for Prostate Cancer (PCa) involve targeting the Androgen Receptor (AR) with hormone therapies like Enzalutamide. Although initially effective, treatment resistance ultimately develops due to mechanisms that circumvent canonical AR signalling, highlighting the urgent need for novel therapeutics. Unfortunately, drug development processes are slow and new methods are needed to accelerate the clinical development pipeline. One such way includes the development of new methods to facilitate efficient drug screening processes and drug repurposing.

We examined zebrafish (Danio rerio) as a model organism for oncology drug screening. Using the 22Rv1 (hormone therapy resistant) cell line, we developed a juvenile Zebrafish Cell-line-derived Xenograft (ZCX) model. Fluorescently stained cells were injected into the perivitelline space of the zebrafish at 48 hours post fertilisation and observed for 72 hours. This allowed for the visualisation of tumour growth and metastasis formation in response to different treatment types in a 5-day window.

Previous data in the lab has identified the targeting of AR co-regulators as a potential treatment avenue. We examined the toxicity of 5 AR and co-regulator inhibitors on zebrafish larvae viability: EPI-7170 (AR inhibitor), CCG1423 (SRF inhibitor), Lestaurtinib (SRF inhibitor), Ipatasertib (AKT inhibitor) and Alpelesib (PI3K inhibitor). The results showed that the inhibitors, excluding CCG1423, were tolerable in the zebrafish models at in vitro IC50 values.

To conclude, the optimisation of the ZCX model could facilitate rapid drug screening and can highlight promising drugs to take forward into pre-clinical trials, thus accelerating the development of novel therapeutics for the treatment of PCa.

Keywords: Zebrafish xenograft, Prostaste cancer, Drug discovery

P-15

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Conference Theme: Experimental Pharmacology

Abstract Title:

The Role of Glucose in Modulating Macrophage Plasticity in Early Diabetes-associated Atherosclerosis

Abstract Text

Introduction

Type-2 diabetes has become increasingly prevalent worldwide, leading to vascular complications, such as atherosclerosis, characterised by lipid-rich plaques within the vasculature, giving rise to major adverse cardiovascular events.

Aim

Using THP-1-derived macrophages, we set up an in vitro model of early diabetes-associated atherosclerosis (DAA) to test the effect of glucose-lowering medications, combined with pro-resolving mediators.

Methods

THP-1 monocytes (Mo) are differentiated into macrophages (MF) using M-CSF (100ng/ml) whilst being exposed to a glucose-challenge (5-25 mM), over 1-week. The expression of inflammatory and cell markers are then measured to study the progression of DAA. RT-qPCR is used to assess the transcriptomic response of macrophages following glucose-stimulation. Viability (MTT) and cytotoxicity (LDH) assays are also conducted on monocytes to evaluate their health within the diabetic environment.

Results

Increasing glucose (up to 20mM) enhances monocyte proliferation by 2.5-fold ($p<0.001$), without increased toxicity (MTT and LDH assays).

At the RNA level, in monocytes, CD14 (Monocyte-marker) is greater expressed than CD68 (Macrophage-marker) with low-glucose; whilst this effect is less apparent with high-glucose. GLUT-1 (glucose-transporter) expression remains unchanged, supporting its constitutive role. We observe a counter-regulatory anti-inflammatory role of TRAIL, with it being massively (>10-fold) upregulated with high-glucose, despite IL-1β and TNF expression remaining low.

In differentiated macrophages, CD14 expression is lower than CD68 in immature-MF (low-glucose), and equally expressed in mature-MF (high-glucose), suggesting enhanced activation. Transition towards a non-classical-MF phenotype is indicated by high CD163 expression.

This alternative-MF presents lower GLUT-1 ($p<0.01$) and MCP-1 (suggesting a critical monocyte role). IL-1β is slightly upregulated by high-glucose, possibly counteracting TRAIL, and thus confirming the crucial role of TRAIL in Mo.

Summary

High-glucose accelerates monocyte differentiation into an alternative-MF, counteracting persistent low-grade inflammation.

Conclusion

The presence of diabetic levels of glucose distinctly reprogrammes the monocyte/macrophage activation and inflammatory response in an in vitro model of DAA.

Keywords: Diabetes; Atherosclerosis, Macrophage plasticity

P-16

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Conference Theme: Experimental Pharmacology

Abstract Title: Salicylaldehyde benzoyl hydrazone as a potential multifunctional therapeutic for neurodegenerative diseases

Abstract Text

Introduction: Neurodegenerative diseases are associated with complex pathological changes in the brain. These include chronic inflammation due to uncontrolled microglial activation and oxidative stress-mediated neuronal cell death. Salicylaldehyde benzoyl hydrazone (SBH) is a Schiff base compound that functions as a tridentate chelating agent, with specific affinity for iron. It has shown efficacy as an anti-bacterial agent, and readily complexes with transition metals. More recently, promising anti-inflammatory and anti-oxidant properties have also been revealed. This study sought to explore whether SBH may exert neuroprotective properties, *in vitro* and *in vivo*.

Methodology: BV2 microglia were challenged with lipoteichoic acid (LTA; 5µg/ml), in the presence and absence of SBH (10µM). Inflammatory changes were measured by the release of nitrite (Griess assay) and pro-inflammatory cytokines TNFα and IL-6 (ELISA). SH-SY5Y neurons were exposed to H_2O_2 and co-incubated with SBH. 4 dpf zebrafish larvae were exposed to lipopolysaccharide (LPS; 20µg/ml; 24h) in the presence and absence of SBH (10µM). Larvae were assessed for survival and evidence of toxicity, indicated by gross morphological malformations and loss of the touch startle response.

Results: LTA exposure significantly enhanced expression of NO, TNFα and IL-6. Co-incubation with SBH significantly attenuated nitrite and TNFα, compared with LTA alone. H_2O_2 promoted cytotoxicity of SH-SY5Y cells which was significantly alleviated by co-application with SBH. Exposure to LPS reduced survival of zebrafish larvae and increased the incidence of morphological malformations relative to controls, alongside an impairment in the touch startle response. Co-application of SBH significantly improved survival, reduced the incidence of morphological malformations, and restored touch startle response when compared with LPS alone.

Conclusions: SBH alleviated microglial activation and oxidative stress-induced neurotoxicity. Exposure to SBH restored the negative impact of LPS-induced inflammation in zebrafish larvae *in vivo*. These findings support the further exploration of SBH as a potential multifunctional therapeutic for neurodegenerative disease.

Keywords: neuroinflammation; neuroimmunology;

P-17

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Conference Theme: Clinical Pharmacology

Abstract Title: NEONATAL MEDICATION SAFETY INFORMATION – A SCOPING REVIEW

Abstract Text

Understanding the pharmacology profile of neonatal drugs are critical to the management of neonates who vomit after drug intake, as vomiting could affect medication absorption and efficacy, potentially leading to therapeutic failures or adverse effects. Current literature provides limited guidance on adjusting medication regimens or dosages in such cases. This scoping study reviewed studies on neonatal pharmacology and drug absorption to inform clinical knowledge. In the current study a reproducible search protocol for commonly administered neonatal drugs was developed, and relevant data was gathered from established search terms. Findings revealed that data on the safety and pharmacokinetic profiles of neonatal medicines were often limited or inconclusive. Key drugs reviewed included paracetamol, sodium feredetate, folic acid, multivitamins, vitamin D supplements, and furosemide. Paracetamol was effective for pain and fever management, though careful dosing was crucial due to immature drug metabolism and risk of hepatotoxicity. Sodium feredetate, used for iron deficiency anaemia, lacked sufficient clinical data on its pharmacokinetics and absorption in neonates. Vitamin supplementation, including folic acid, calcium, and colecalciferol was considered important during preconception and pregnancy, although specific dosing data and safe upper limits were limited for neonates. Furosemide, used to manage fluid overload, presented dosing and monitoring challenges due to the risks of electrolyte imbalance and ototoxicity.

Overall, this review highlights limitations in effective neonatal pharmacotherapy, emphasising the need for targeted studies to enhance therapeutic outcomes and medication safety. Efforts in future research should aim to improve pharmacokinetic data profiles, develop predictive models for drug absorption and establish accurate dosing guidelines to optimise neonatal care and address challenges such as vomiting after drug intake.

Keywords: Neonatal pharmacotherapy,

P-18

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Conference Theme: Clinical Pharmacology

Abstract Title: An Audit of Best Medical Therapy Among Patients with Carotid Artery Stenosis Attending a Tertiary Stroke Centre

Abstract Text

Background
Carotid artery stenosis (CAS) is estimated to cause 11-28% of ischaemic strokes annually. The primary objective of this audit was to assess current prescribing adherence to best medical therapy (BMT) to patients with CAS in a tertiary stroke centre. Our secondary aim was to assess stability, regression or progression of CAS whilst on BMT.
Methods
A retrospective chart review was conducted in a tertiary stroke centre over a six week period. Patients were included if they were aged over 18 years, presenting to an outpatient stroke clinic, and had a known diagnosis of either symptomatic or asymptomatic CAS. The European Stroke Organisation Guidelines were used to define BMT.
Results
A total of 56 charts were reviewed at three weekly outpatient clinics. Of the 27 patients meeting our inclusion criteria 66% (n=18) were male, median degree of CAS was 50-70% and 78% (n=20) had symptomatic CAS. 89% were on BMT but only 56% achieved a low-density lipoprotein cholesterol (LDL-C) target of <1.8mmol/L (median 1.6mmol/L (range:0.7-4.2mmol/L) and only 66% (n=18) had a documented smoking status.
81% of patients with symptomatic CAS on BMT had stable stenosis, 5% had regression and 14% had progression of stenosis. 50% of asymptomatic patients had progression of the degree of their stenosis.
Conclusion
Overall adherence to BMT was good at 89% but there is room for improvement particularly in terms of lipid target level and documentation of risk factor status. BMT resulted in stable stenosis and low progression rates particularly in patients with symptomatic CAS.
BMT and early detection are essential for management to control progression of CAS but we have highlighted the opportunity to improve LDL-C targets. Further research is needed to evaluate if the results of this study are translatable to the stroke population in general.

Keywords: Best Medical Therapy, Carotid Artery Stenosis, Pharmacological Management

P-19

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Conference Theme: Clinical Pharmacology

Abstract Title:

The Impact of EAST-AFNET on Anti Arrhythmic Drug Claims in Ireland: An Analysis of Trends from 2014 to 2023

Abstract Text

Introduction:
The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET), published in August 2020, reported a significant reduction in cardiovascular (CV) death and stroke in patients receiving early atrial fibrillation (AF) rhythm control, of which most received anti arrhythmic drugs (AADs) alone. Based on this, some have called for a shift in the focus of AF care to minimizing AF burden, to optimise temporal AF outcomes. No population-based studies looking at (AAD) prescription rates have been studied past 2018.

Objective:
To determine the impact of the EAST-AFNET trial on AAD claim rates in Ireland.

Methods:
Data on AAD claims were obtained from 1st January 2014 to 31st December 2023 using the Primary Care Reimbursement Services databases. AADs, identified using WHO ATC codes, included flecainide, propafenone, amiodarone, dronedarone and sotalol. To determine the claim rate, data is presented as total number of patients/1000 population. A segmented regression analysis was performed to identify the impact of the EAST-AFNET trial on AAD claims since 2021. The change in slope of AAD claims after EAST-AFNET publication is presented as β.

Results
Total annual AAD claims increased significantly after the publication of EAST-AFNET (β = 0.957, p = 0.025, 95%CI [0.03 – 0.34]). This was driven by significant increments in flecainide and propafenone (β = 0.418, p = 0.012, 95%CI [0.012-0.017] and β2 = 1.813, p = 0.001, 95%CI [0.013 – 0.033] respectively). Amiodarone claims, which were declining pre-2021, also significantly increased (β = 1.269, p = 0.003, 95%CI [0.042 – 0.128]). There was no significant change in sotalol and dronedarone claim rates (β = 0.322, p = 0.463, 95%CI [-0.44 – 0.86] and β = 0.174, p = 0.69, 95%CI [-0.19 – 0.26]).

Conclusion:
The rate of total annual AAD claims increased significantly after the publication of EAST-AFNET. This was driven by significant increases in flecainide, propafenone and amiodarone claims, with no change seen in sotalol and dronedarone claims.

Keywords: Anti-Arrythmic drugs; Atrial Fibrillation; EAST-AFNET

P-20

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Conference Theme: Clinical Pharmacology

Abstract Title: Polypharmacy: An Age-Old Problem

Abstract Text

Background: The anticipated doubling of the world's population aged ≥ 65 between 2019 and 2050 (1) will be accompanied by a rise in polypharmacy (concurrent use of five or more medications). Polypharmacy has been associated with increased frailty, risk of falls, potentially inappropriate medication use, hospitalizations and mortality. The aim of our study was to determine the prevalence of polypharmacy and determine any factors associated with it in a subset of very old adults from a prospective cohort study.

Methods: A secondary analysis was performed of prescribing data for a subset of the oldest old participants (aged ≥80) from a prospective cohort study conducted in patients aged ≥ 65 presenting to the emergency department (ED) of an Irish university teaching hospital (n=421). Paired t-tests were performed to determine the significance of differences between patients with and without polypharmacy.

Results: Rates of polypharmacy and hyperpolypharmacy (≥ 10 medications) among our subset of 143 patients were 77%, and 29% respectively. The median number of medications per patient was 7. The five commonest ATC codes among patients with polypharmacy were B01 Antithrombotic agents, A02 Drugs for acid-related disorders, C10 Lipid modifying agents, C03 Diuretics and C07 Beta blocking agents. Patients with polypharmacy had significantly ($p<0.05$) higher levels of comorbidity and frailty and lower levels of functional independence. They also had higher 3 month fall incidence, although there was no significant difference demonstrated when it came to 30 day mortality or levels of ED attendance and unexpected hospital visits.

Conclusion: We demonstrated high rates of polypharmacy in very old adults attending the ED of an Irish teaching hospital. Traditional ED models of care are not equipped to assess and treat multimorbid older adults with polypharmacy. It is therefore essential to develop new systems with access to multidisciplinary teams that incorporate medicines optimisation and take into consideration the impact of multimorbidity and frailty on acute presentation.

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Keywords: Polypharmacy; Geriatrics

P-21

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Conference Theme: Clinical Pharmacology

Abstract Title: Audit of Door-Needle-Times and Inpatient Stroke Care in an Irish University Teaching Hospital in 2023

Abstract Text

Background: Stroke is a leading cause of adult disability and death in the European Union (1). Our study aims to benchmark stroke care in an Irish university teaching hospital against national audit findings (2) in order to inform quality improvement initiatives to address areas for potential improvement.

Methods: HIPE data for all patients assigned principal ICD-10 codes I61 (Nontraumatic intracerebral haemorrhage), I63 (Cerebral Infarction) and I64 (Stroke, not specified as haemorrhage or infarction) discharged from an Irish university hospital between 1 January and 31 December 2023 were analysed and benchmarked against findings from the 2022 Irish National Audit of Stroke (INAS) Report (2).

Results: A total of 451 patients were included (median age 74). Our centre achieved performance measures that exceeded the national average in the following areas: stroke unit admission rates (69%), proportions of patients receiving a CT brain within an hour of arrival (52%); who had swallow and mood screening (77% and 81% respectively); were assessed by an allied health professional (94%) and discharged via the Early Supported Discharge programme (10.2%). Thrombolysis rates in ischaemic stroke patients were similar at 10%. Areas with potential for improvement as benchmarked with national averages were as follows: median time from arrival to seeing a doctor (15 minutes), door-needle-time (80 minutes), length of stay (11 days), percentage of stay which was in a stroke unit (55%), rate of discharge home (48%), mortality in ischaemic stroke (9.3%) and haemorrhagic stroke (32.7%).

Conclusion: The 2022 INAS Report (2) suggests a target door-needle-time of ≤60 minutes. Our median door-needle-time of 80 minutes necessitates a process evaluation and dedicated quality improvement initiative, as faster door-needle-times are associated with better outcomes. Our centre also requires an increase in dedicated stroke unit capacity, as stroke unit admission is associated with better outcomes for patients.

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Keywords: Stroke; Thrombolysis

P-22

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Conference Theme: Clinical Pharmacology

Abstract Title: An Overlooked Challenge in a Case of Long-Term Antifungal Use: What Lies Beneath?

Abstract Text

Background:

Fluconazole, a widely used antifungal agent, functions by inhibiting the enzyme lanosterol 14α-demethylase, a critical component in the synthesis of ergosterol, which maintains fungal cell membrane integrity. Fluconazole has the potential for drug-drug interactions and adverse effects.

Case:

A 53-year-old woman was admitted for rehabilitation after a prolonged intensive care admission type-2 respiratory failure in the setting of pneumonia requiring intubation. Central venous access was instituted for vasopressor support. Her admission was complicated by a fungaemia.

In ICU, beta-D-glucan levels were elevated with multiple blood cultures showing Candida parapsilosis. Initial was caspofungin and subsequently amphotericin B presuming a central line infection.

She was then transferred to rehabilitation for reversal of post ICU myopathy. Her primary complaint during rehabilitation was ongoing low back pain with mildly elevated MRI confirmed L2-L3 discitis and osteomyelitis. Repeat beta-D-glucan levels remained persistently elevated with normal procalcitonin and blood cultures.

Multidisciplinary discussion (microbiology, radiology and pharmacy) favoured empiric treatment of presumed fungal discitis with prolonged high dose fluconazole, duration pending clinical and biochemical response to treatment.

Over 3-months, she developed symptoms of severe dizziness, fatigue and nausea. Tilt table testing identified a postural drop of 67mmHg.

A Synacthen test revealed baseline cortisol-237 nmol/L and 30-minute cortisol 364-nmol/L. with elevated ACTH, consistent with primary or drug-induced adrenal insufficiency, with no preceding steroid use and no radiological evidence of adrenal pathology.

Discussion:

Fluconazole is postulated to interfere with steroidogenesis by affecting the cytochrome P450 enzyme family, crucial in adrenal hormone synthesis.

Prompt recognition and appropriate steroid replacement are crucial to managing this condition, and discontinuation of the offending agent is essential. In this case, fluconazole dose was reduced but ongoing treatment was deemed essential for fungal discitis, a prescribing cascade was necessary and steroid replacement was required.

P-23

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Conference Theme: Clinical Pharmacology

Abstract Title: Prolonged QT – a red herring

Abstract Text

Introduction
Acquired long QT syndrome is a potential adverse effect of drugs and is associated with polymorphic ventricular tachycardia, a life-threatening arrhythmia. Acutely unwell hospitalised people are at risk of this complication and must be monitored by electrocardiography when prescribed medications with this potential effect.

Case
A 66-year old gentleman with primary progressive multiple sclerosis (MS) was admitted to the high dependency ward with vomiting, acute colonic pseudo-obstruction and aspiration pneumonia. Risk factors for pseudo-obstruction were severe hypokalaemia (serum potassium 2.5), intrathecal baclofen via subcutaneous baclofen pump used to treat severe spinal cord spasticity and spinal cord injury due to MS. His admission was complicated by sepsis, with hypotension requiring vasopressors and fast atrial fibrillation requiring an amiodarone infusion, with ongoing replacement of potassium. Hypokalaemia resulted from vomiting.
The automated electro-cardiograph reading revealed a QTc of 580 ms. Medication review was undertaken to identify all QT prolonging drugs so that these could be discontinued and substituted with safer alternatives. The potential culprits included amiodarone, metoclopramide, venlafaxine, quetiapine and hypokalaemia. Low magnesium levels were replaced.
Meanwhile, ECG morphology was reviewed by a cardiology colleague who identified U waves following the T wave which were precipitated by severe hypokalaemia. U-waves led to the inaccurate automated reading of the QT interval by the computer algorithm. The QT interval was manually measured from the electrocardiograph and was within normal limits.

Conclusion
Computerised interpretation of QTc have demonstrated an overall accuracy of 88%. This may lead to unnecessary readjustment of medications which are otherwise indicated and confirmation by manual QTc measurement must be considered. Basic electrocardiograph interpretation skills are still necessary even with the dawn of artificial intelligence. This case also highlights a potential complication of baclofen associated acute colonic pseudo-obstruction through GABAergic mechanisms.

P-24

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Conference Theme: Clinical Pharmacology

Abstract Title: Audit of Appropriate VTE Prophylaxis Prescribing and VTE Risk Assessment in St. Camillus' Community Hospital

Abstract Text

Background:
Venous thromboembolism (VTE) affects approximately 11,000 people annually in Ireland, with 63% occurring in-hospital or within 90 days post-discharge. Approximately 70% of hospital-acquired VTE cases are preventable with appropriate prophylaxis.

Prompt implementation of the Health Service Executive (HSE) VTE Prophylaxis Protocol upon admission is essential to improve patient safety

Aim:
To assess adherence and compliance with VTE risk assessments and prophylaxis prescribing in patients aged ≥18 during their admission at St. Camillus' Hospital, in line with HSE and National Institute for Health and Care Excellence (NICE) guidelines.

Objectives:

To evaluate whether adult patients admitted to a Community Rehabilitation Hospital underwent VTE risk assessments and were prescribed appropriate VTE prophylaxis before implementation of a new Medication Kardex. The proposed Kardex includes a standardised VTE risk assessment tool and guidance on prescribing appropriate prophylaxis, founded on the National VTE Prophylaxis Protocol, developed and approved by University Hospital Limerick Group Drug and Therapeutics Committee.

Methodology:
In September 2024, medical records of all 28 in-patients in St Camillus' Community Hospital were reviewed using the newly introduced VTE risk assessment tool. The review focused on appropriate prophylactic enoxaparin sodium prescribing and instances of therapeutic duplication. Results were compared against the NICE Guidelines for Venous Thromboembolism Prevention.

Results:
Of the 28 cases, 29% were appropriately prescribed enoxaparin sodium, 36% had inappropriate omissions and 4% had appropriate omissions. In 32%, enoxaparin was withheld appropriately due to DOAC use. No cases of duplicate anticoagulant prescribing were observed.

Conclusions:
There is scope for significant improvement in ensuring VTE prophylaxis is prescribed in appropriate patients. Our recommendations based on this information include a repeat audit following implementation of the proposed Kardex which includes integrated VTE risk assessment and guidelines, increased education of staff, and the admission of a section to the Kardex detailing reasons for omission of prophylaxis.

Keywords: VTE; Kardex;Audit.

P-25

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Conference Theme: Clinical Pharmacology

Abstract Title: Medications Sometimes Don't Cut It.

Abstract Text

Introduction

The development of a high-output stoma is associated with nutritional and electrolyte disturbances along with fluid imbalance which can lead to rapid clinical deterioration.

Case presentation

We present the case of a 82 years old lady with ileostomy, post ilio-caecal resection and right hemicolectomy for bowel perforation due to colon cancer. Stoma output was persistently elevated at 2-3 litres in the post-operative period with electrolyte imbalance including persistently low magnesium and acute pre-renal dysfunction. Stool samples were negative for enteric pathogens.

Multidisciplinary care involved dietetics, stoma nurse, older persons advanced nurse practitioner and general surgery. Non-pharmacological approaches to stoma management including low fibre diet and reduced free water, tea, coffee (hypotonic fluids) intake, reduced water intake with meals, with oral rehydration using high sodium content St Marks solution ($NaHCO_3$ and glucose). Dioralyte oral hydration fluid was avoided due to hyperkalaemia. Intravenous hydration for maintenance fluids (30mls/kg/day) and replacement of fluid losses along with electrolyte replacement for low magnesium was continued.

The anti-motility agent loperamide, which acts on the opiate receptors, was titrated to supra-therapeutic unlicensed doses of 86mg. Loperamide was switched to capsules once the dose was escalated >24 mg to avoid excess sorbitol. Twice daily omeprazole was used to reduce gastric secretions. In addition, codeine phosphate 30mg qds pre meals was commenced without stoma output reduction. Octreotide was added for enhanced anti-secretory efficacy without benefit. Bile acid binders (cholestyramine) and pancreatic enzyme replacement failed to provide benefit. Metoclopramide was avoided due to pro-kinetic properties. Ondansetron (added as an anti-emetic) was discontinued due to prolonged QTc interval. A peripheral inserted central catheter was in situ to support intravenous fluids and total parenteral nutrition. After 8 weeks, with failure of medical therapy, stoma reversal was undertaken as a last resort.

Conclusion

Pharmaceutical approaches are considered central to stoma management after bowel resection, and this requires multidisciplinary / cross-specialty collaboration. However, high output stoma may be resistant to maximum medical treatment and require surgical stoma reversal.

Keywords: high-output stoma, pharmacological, non-pharmacological approach

P-26

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Conference Theme: Clinical Pharmacology

Abstract Title: Navigating the Pressure: paradox of hypertension and orthostatic hypotension

Abstract Text

Introduction

Orthostatic hypotension is increasingly recognized as a common co-morbidity in older adults often occurring in conjunction with hypertension and complicating its management.

Case

We present the case of a 78 year old lady with recurrent dizzy spells, exacerbated by position changes, intermittent syncope over 4 years with injurious falls and a Colles' fracture.

A head up tilt test was demonstrated severe orthostatic hypotension, with a systolic BP drop of -54 mmHg. The head up tilt test was aborted after 1 minute due to near syncope. Midodrine was commenced titrating from 2.5mg three times daily to 10mg three times daily based on normal sitting clinic BP readings. An ambulatory BP monitor revealed severe hypertension and following variability in readings was observed:

Maximum Systolic BP 220 mmHg

Maximum Diastolic BP 157 mmHg

Average overall 153/91 mmHg

Daytime mean 149/94 mmHg

Nighttime mean 169/80 mmHg

Non-pharmacological approaches included abdominal compression with a corset, increased fluid intake particularly prior to getting out of bed and rising the head of the bed. No further syncope was noted with addition of these measures along with midodrine. Concern was present regarding potential complications of supine hypertension and intermittent episodes of alarmingly high BP readings. Medications known to aggravate orthostatic hypotension were avoided (e.g. alpha blockers, beta-blockers, nitrates). Low dose angiotensin receptor blocker was commenced at nighttime without reoccurrence of syncope. The rationale was to reduce renin-aldosterone system activation cause by daytime renal hypoperfusion along with lowering nighttime natriuresis. Result of repeat BP monitoring are awaited.

Conclusion

Tailoring therapy to minimize risk while maintaining BP control is complex and further research is required to inform clinical practice.

P-27

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Conference Theme: Clinical Pharmacology

Abstract Title: Fabrazyme: Can It Prevent Stroke?

Abstract Text

Background

Fabry disease is an X-linked lysosomal storage disorder with multi-system manifestations. It is the second most common monogenic cause of stroke and occurs due to alpha-galactosidase deficiency with a frequency of 1:20,000 in the population.

Case Presentation

A 47-year-old Ukrainian male with Fabry disease was referred to rehabilitation after left middle cerebral artery infarction in a small vessel distribution. There was no evidence of large vessel occlusion. This was treated acutely with alteplase. He was on agalsidase-beta replacement for Fabry disease diagnosed at 7 years of age. Risk factors included cannabis and cigarette smoking. Secondary stroke diagnostic assessment was unremarkable with prolonged cardiac rhythm monitoring, carotid imaging and echocardiogram with bubble study. Hypertension was well controlled with normal ambulatory 24-hour blood pressure. Complications of Fabry disease in this case included sub-nephrotic range urine proteinuria, stable stage 3a chronic kidney disease and left ventricular hypertrophy, sensori-neuronal hearing loss, and angiokeratomatous lesions involving both limbs and back.

Conclusion

This case highlights potential competing aetiologies for vasculopathy including Fabry disease, cannabis and cigarette smoking along with hypertension/chronic kidney disease related arteriosclerosis. This patient was on enzyme replacement therapy, Fabrazyme. On review of the literature, while this therapy reduces renal complications, it also protects against stroke to a certain extent. Additionally, it is debatable whether a bubble study to assess for patent foramen ovale, should have been performed in this case, given the small vessel aetiology and other competing mechanisms.

P-28

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Conference Theme: Clinical Pharmacology

Abstract Title: Renal Tubular Injury BMs in the identification of sub-clinical AKI and DIKI – IMI/SAFE-T/TransBioLine

Abstract Text

Background: Drug-induced kidney injury (DIKI), a subphenotype of acute kidney injury (AKI), is a common adverse effect of cisplatin chemotherapy. Current functional biomarkers (BMs) have limitations in the detection of renal tubular injury (a hallmark of DIKI), and the 23rd ADQI consensus conference proposed using novel BMs to enhance the diagnostic criteria for AKI.

Methods: In this prospective study, 105 cisplatin-treated patients (Treated), 20 non-cisplatin-treated cancer controls (Non-Treated), and 34 Healthy controls were enrolled. Blood and urine samples from the Treated group were collected at specified timepoints. Standard BMs and novel BMs (eight urinary, one serum) were assessed. Three blinded nephrologists adjudicated the presence or absence of DIKI in cisplatin-treated

patients. BM accuracy was defined by sensitivity, specificity, AUROC, and changes (absolute and percentage) from baseline were compared between groups, with median time to peaks calculated.

Results: All biomarkers showed significant changes from baseline in the Treated group versus Non-Treated group. Most urinary BMs effectively detected cisplatin exposure (AUROC > 0.8). Novel BMs peaked earlier with α-GST peaking first (Day 1), followed by serum CYSC and KIM-1 (Day 2). Treated group were adjudicated into DIKI (N = 24) and No-DIKI (N = 71) groups. Significant differences were observed in all BMs between both

DIKI and No-DIKI groups compared to controls. No significant differences were found in urinary BMs, except for neutrophil gelatinase-associated lipocalin and cystatin-C, between DIKI and No-DIKI groups.

Conclusion: Novel BMs detected DIKI earlier and more sensitively than standard BMs. A panel of BMs is likely superior for comprehensive nephrotoxicity assessment, which aligns with FDA's 2018 qualification letter supporting novel BMs with standard BMs in phase 1 drug development.

Keywords: Acute Kidney Injury; Cisplatin; Biomarkers

P-29

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Conference Theme: Pharmacy/Pharmacology Education

Abstract Title: Neonatal Medication Safety Information – A Scoping Review

Abstract Text

Background: One in seven infants is born prematurely with underdeveloped organ systems, necessitating complex medical care in Neonatal Intensive Care Units. The Family Integrated Care model involves parents in medication administration to improve neonatal outcomes and reduce parental anxiety during hospital stays. Neonates' unique and rapidly evolving physiology impacts drug absorption, resulting in variable medication safety and efficacy. This scoping study reviewed the neonatal pharmacology of commonly administered medicines and the impact that vomiting after drug intake may have on the therapeutic outcomes of neonates.

Results: The data on neonatal medicines' safety and pharmacokinetic profiles were often limited or inconclusive. Paracetamol used in the management of pain and fever requires careful dosing due to the immature drug metabolism of neonates and the risk of hepatotoxicity; sodium feredetate used for the management of iron deficiency anaemia lacks sufficient data on its pharmacokinetics profile in neonates; vitamin supplementation, including folic acid, calcium, and colecalciferol, is primarily focused on dosing during preconception and pregnancy, with limited data on safe upper limits for neonates; finally, furosemide used for fluid overload presents dosing and monitoring challenges due to risks of electrolyte imbalance and ototoxicity.

In addition, vomiting after drug intake affects medication absorption and efficacy, potentially leading to therapeutic failures or adverse effects. Current literature has limited pharmacokinetic profiles on commonly administered neonatal medicines and guidance on medication adjustments after vomiting. The PADDINGToN resources address these issues by providing detailed drug information and safety guidelines for clinicians and parents.

Conclusion: Future research should be directed towards improving pharmacokinetic data profiles of medicines and medication safety in neonates. Establishing accurate dosing guidelines will further optimise neonatal care and address the challenges and limitations related to neonatal pharmacotherapy, in particular, vomiting after drug intake.

Keywords: Neonat*, Neonate, Neonates, Babies, Infants

P-30

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Conference Theme: Pharmacy/ Pharmacology Education.

Abstract Title: Assessment of rates of polypharmacy in a University Hospital in the MidWest of Ireland and correlating clinical outcomes in those aged 65 and older

Abstract Text

Introduction

Polypharmacy is defined by the WHO as the concurrent use of five or more medications. Globally the prevalence of polypharmacy is set to rise as the population ages and more people suffer from multiple long-term conditions. As per the regional population profile conducted in March 2024 the MW has an older population compared to the rest of Ireland and this is predicted to continue to grow. Ensuring medication safety in polypharmacy is one of the key challenges for medication safety in our day to day work activities.

Methods

We assessed the inpatient medication records of a total of 35 patients across 14 medical wards over a two day period. The medical wards assessed did not have a clinical pharmacist assigned to them at the time of the audit. Only patients aged 65 and older were included in the data collection. The number of medications was checked and only patients taking five medications or more were assessed for potential drug interactions.

Results

Of the 35 patients assessed 20 were female and 15 male. The mean age of patients assessed was 80 years old. Of these 35 patients 78% (N= 27) did not have a medication reconciliation performed by a member of the multi disciplinary team. Of the patients that did not have a medication reconciliation carried out 16 (17%) were found to have potential drug interactions.

Conclusions

We have identified from this audit that the assessment of polypharmacy in an acute Hospital setting is imperative to improve polypharmacy rates and prevent drug- drug interactions. We will be conducting an educational session on polypharmacy, the importance of a medication reconciliation at time of admission and common drug interactions at our geriatric teaching session and plan to re audit these medical wards in the three months to re assess outcomes.

Keywords: polypharmacy, clinical outcomes

P-31

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Conference Theme: Pharmacy/Pharmacology Education

Abstract Title: Evaluating student understanding of the core concepts of pharmacology

Abstract Text

Introduction: Both educators and graduates have expressed concern about a perceived pharmacology knowledge gap that includes difficulty applying fundamental principles to clinical and research problems. Consequently, we sought to determine the extent to which current students can define and apply a subset of core concepts and to identify any misconceptions arising from the responses.

Methods: Of the twenty-four pharmacology core concepts emerging from a recent international collaboration, four pharmacokinetic (PK) and four pharmacodynamic (PD) concepts were chosen, namely drug bioavailability, drug clearance, volume of distribution, steady-state concentration, drug efficacy, drug-target interaction, drug tolerance, and structure-activity relationship. Globally, a total of 318 students from 11 universities completed the PK quiz, while 218 students from 10 universities completed the PD quiz. Expert analysts identified the essential elements for each concept and then independently assessed each student response. In pairs, experts compared their evaluations to reach a consensus and then grouped misconceptions thematically.

Results: Less than 30% of students provided a definition encompassing all essential elements for each core concept. For the PK concepts, participants found drug clearance most challenging, generally conflating it with the rate of elimination, whereas they demonstrated a better understanding of drug bioavailability. From the PK quiz, 34 misconception themes were identified, with volume of distribution and drug clearance producing the highest numbers (13 and 12, respectively). For the PD quiz, drug efficacy was the core concept with which students struggled most, and 55 misconception themes were identified.

Conclusion: Overall, results suggest that students found it easier to apply the concepts than to define them, which might reflect the shift from didactic to active learning approaches. These findings may be useful for educators who are developing introductory pharmacology courses by providing conceptual focus and revealing common misconceptions to explicitly address.

Keywords: Core Concepts, student understanding, misconceptions

P-32

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Conference Theme: Pharmacy/Pharmacology Education

Abstract Title: Asynchronous video-recorded lectures to replace face-to-face teaching: A mixed methods study.

Abstract Text

Background: Recorded video lectures are increasingly provided, replacing live lectures, utilising currently available technology for online education. Little however is known about the impact of recorded video lectures on student engagement and their examination performance. This study aims to understand whether a correlation exists between medical student engagement with recorded teaching and subsequent examination performance in pharmacology discipline. A further aim is the exploration of faculty experiences in the production and provision of asynchronous video-recorded lectures.

Methods: This mixed methods approach quantitatively analyses the responses of 144 Year 2 medical students to questions relevant to the topics related to the content of the produced asynchronous video-recorded lectures, within the summative assessment. The relationship of these variables is further tested with Pearsons correlation coefficients. Inductive thematic analysis was performed on transcripts from recorded semi-structured interviews with six faculty members who had produced video-recorded lectures. Lecturer experiences in video production, their technical needs, challenges and recommendations were explored in-depth.

Result: Based on the data, students were divided into two groups; those who viewed (viewers) and never viewed (non-viewers) the video recordings. A positive relationship was identified between those who viewed the pharmacology topic related videos and their performance in the related exam question. Viewers performed significantly better but definitely not worse than non-viewers. The qualitative data further shows that the experience of video lecture production enhanced Faculty's technical skills, hence enabling successful video posting and identifying appropriate pedagogical support which are deemed important factors for remote learning.

Conclusions: Asynchronous video-recorded lectures can contribute towards successful remote teaching of medical students. However, Faculty needs technical support not just to produce an educational video but one that is underpinned by digital pedagogy since teacher presence has a positive impact on student engagement.

Keywords: Remote Teaching; video-recorded lectures; pharmacology

P-33

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Conference Theme: Other

Abstract Title: Clinical treatment and outcomes for ischaemic strokes in the oldest old: a retrospective cohort study over a 12 month period

Abstract Text

Stroke is the third leading cause of death and a leading cause of acquired neurological deficit in Ireland. Acute stroke thrombolysis is recommended regardless of age and pre-morbid disability by the European Stroke Organisation. We aimed to evaluate stroke treatment and outcomes in the oldest old to inform decision-making and patient counselling for stroke intervention.

Methods

Data was collected by specialist stroke nurses for all acute stroke patients (inclusive of community and in-hospital strokes) admitted to a university teaching hospital for the Irish National Audit of Stroke (2023). Data was examined to establish access to thrombolysis and thrombectomy and outcomes for a cohort of patients aged ≥ 80 years.

Results

There were 559 acute stroke patients admitted in 2023. Overall mortality for ischaemic stroke was 8.2% (n=40). Thrombolysis was administered to 10.8% (n=53) and 8.6% (n=42) underwent a thrombectomy. Nearly a third of acute stroke patients (31.8%, n=178), were ≥80 years. Ischaemic stroke subtype accounted for 88.2% (n=157). In this cohort ≥80 years, ischaemic stroke mortality was 16.8% (n=30), thrombolysis rate was 9.5% (n=17), thrombectomy rates were 3.4% (n=6), with symptomatic intracranial haemorrhagic complications in 1 patient. Adults aged ≥80 who received thrombolysis had a pre-morbid mRS ranging from 0-3, with one fifth being independent pre-admission, 20.7% with mRS of 0 (n=11). Post-stroke mRS on hospital discharge ranged from 1-6, with a mortality rate of 11.3% (n=6) in those that received thrombolysis. Six patients ≥80 years underwent thrombectomy, the majority of whom were independent pre-stroke with mRS of 0 in 83% (n=5). On discharge the mRS was between 2-5 in 83% (n=5), with one death.

Conclusion

Access to acute stroke thrombolysis is recommended regardless of age and thrombolysis rates are comparable to young cohorts. Thrombectomy access is lower and further analysis is necessary to assess the underlying cause (e.g. stroke severity or aetiology related). Haemorrhagic complications were uncommon.

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Conference Theme: Other

Abstract Title: Investigating the circular RNA expression profiling in damaging alveolar epithelial Type II cells in pulmonary fibrosis

Abstract Text

Pulmonary fibrosis is a progressive interstitial lung disease characterized by lung scarring, largely driven by the injury of alveolar epithelial type II (AT2) cells. The mechanism of AT II damaging is not clearly understood. However, the emerging evidences suggested that circular RNAs (circRNAs) may play a critical role in this process. Our lab used a novel model of pulmonary fibrosis, induced pluripotent stem cell-derived AT2 (iAT2) cells from patients, which showed that circRNA are dysregulated in pulmonary fibrosis through microarray analysis.

In this study, we aimed to further investigate the expression and function of circRNAs in AT II with the ultimate goal of exploring their therapeutic potential in pulmonary fibrosis. Seventeen circRNAs, identified from the preliminary microarray data, were selected for further validation using qRT-PCR in the iAT II model (SFTPC mutant vs corrected). Only One circRNA (hsa_circ_0077520) was significantly downregulated in fibrotic iAT II cells, consistent with the previous microarray findings.

We further explored circRNA expression, to provide mechanistic insights into their role in pulmonary fibrosis, in an alternative AT2 model, the SALI model and corrected iAT II spheroids where cells were treated with a pro-fibrotic (PF) cocktail at 48, 72, and 96-hour intervals. 72 hr time point showed best response of fibrotic stimuli. Only circRNAs were detected in SALI model and corrected iAT2 spheroids. The results from iAT2 model (mutant vs corrected) and PF treated iAT2 spheroids model showed that three circRNA namely, has_circ_ 0001110, has_00077520 and has_circ_0003768 showed same trend of downregulation in both SFTPC-mutant vs corrected in qRT-PCR and corrected iAT2 spheroids treated with PF cocktail. These results suggest a time-dependent response of circRNA expression to fibrotic stimuli. Based on these results, hsa_circ_ 0001110, hsa_00077520 and hsa_circ_0003768 were chosen for biochemical characterisation to ensure their true circular form. Our findings provide critical insights into circRNA expression in human models of AT2 cells and iAT2 spheroids, highlighting the potential of circRNAs as therapeutic targets for pulmonary fibrosis.

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Conference Theme: Other

Abstract Title: Comparative Efficacy of HDAC Inhibitors in Modulating GPC2 and MHC Class I and II Expression

Abstract Text

Background: Histone deacetylase inhibitors (HDACis), such as Vorinostat, have shown potential in modulating tumour associated antigens and influencing MHC class I and II expression in dendritic cells (DCs). This study aims to investigate the impact of the FDA approved HDACis on Glypican-2 (GPC2) and MHC class I and II expression to explore their potential in enhancing anticancer vaccine efficacy through improved antigen presentation.

Methods: DC2.4 and neuroblastoma cell lines (Kelly and KellyCis83) were treated with various concentrations of Vorinostat (0.01 to 2 µM) to determine IC50 values using an acid phosphatase assay. Statistical analysis was performed using one-way ANOVA.

Results: We evaluated the efficacy of Vorinostat, Panobinostat, and Entinostat in DC2.4, Kelly, and KellyCis83 cell lines by determining IC50. In DC2.4 cells, Vorinostat had an IC50 of 0.67 µM (p-value < 0.0001), Panobinostat - 0.13 µM (p < 0.0001), and Entinostat - 1.95 µM (p-value < 0.0001). The highest fold resistance was observed for Entinostat, with a 17.9-fold increase compared to Panobinostat. In KellyCis83 cells, Vorinostat had an IC50 of 1.13 µM (p-value = 0.005), Panobinostat - 0.025 µM (p = 0.0053). The highest fold resistance was 56.5-fold for Vorinostat compared to Panobinostat.

Conclusion: Panobinostat demonstrated highest potency in growth inhibition with the lowest IC50 values across the cell lines. Notably, the greatest fold resistance was observed for Entinostat in DC2.4 and Kelly cells. Further investigation will examine the impact of these HDAC inhibitors on GPC2, MHC I, and MHC II expression.

Keywords: GPC2, MHC1, HDAIC

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Conference Theme: Other

Abstract Title: Ocrelizumab Case Study

Introduction

Disease-modifying therapies have revolutionized the management of multiple sclerosis (MS). Ocrelizumab is a recombinant human anti-CD20 monoclonal antibody effective in reducing disease progression in primary progressive MS. Understanding its pharmacological and biological mechanisms is essential to anticipate potential adverse effects in clinical practice.

Case

A 53-year-old gentleman presented with worsening respiratory symptoms over a 4-week period, having tested positive for COVID-19 via antigen testing at the onset of his illness, with PCR confirmation upon admission. A chest X-ray showed patchy bilateral lower zone interstitial infiltrates. The patient had been on long-term nitrofurantoin for recurrent urinary tract infections.

His COVID-19 was initially treated with antibiotics, dexamethasone, and remdesivir. However, remdesivir was discontinued after 3 days due to rapidly rising ALT levels.

The patient initially improved with treatment, but over the following week, his respiratory symptoms and fever recurred, along with herpetic-like stomatitis. His fever was unresponsive to broad-spectrum antibiotics and acyclovir. A CT thorax scan showed progressive COVID-19 pneumonitis, and the cycle threshold (CT) value for COVID-19 remained low, indicating ongoing viral replication. A multidisciplinary discussion with microbiology and pharmacy took place. His fever only resolved after remdesivir and dexamethasone were restarted, with close monitoring of liver function tests.

Conclusion

This case highlights persistent COVID-19 infection in an immunosuppressed individual on Ocrelizumab. This therapy causes B-cell depletion, resulting in inadequate cytokine regulation, which may have contributed to the prolonged COVID19 infection. Stomatitis with herpetic-like lesions has been identified as a complication of COVID-19, however in this case herpes simplex virus 1 was detected on an oral swab. Ocrelizumab is associated with other viral infections, such as herpes simplex, varicella-zoster, and hepatitis B virus reactivation.

This symptomatic respiratory illness with pneumonitis was likely due to persistent COVID-19 replication with co-morbid herpes simplex infection without evidence for a a late hyper-immune response. Further immunomodulation with IL-6 inhibitors (e.g., tocilizumab) was not indicated.