Scientific program

Thank you to our sponsors

Principal sponsor

Bellberry Limited
supporting research and ethics

Platinum sponsors

BRITISH PHARMACOLOGICAL SOCIETY

NAPE
National Alliance for Pharmacy Education

Gold sponsors

AFT pharmaceuticals
Working to improve your health

SCIEX
The Power of Precision

Silver sponsors

PKPDRX

Douglas
improving lives

evolve
Better care. Better decision-making. Better use of resources

Bronze sponsors

pharmaceutics
an Open Access Journal by MDPI

BMG LABTECH
The Microplate Reader Company

St. Vincent’s Clinical School
Tuesday 24 November 2020 | 12.00 – 5.15 pm Australian Eastern Daylight Time (AEDT)

12.00 – 12.46  Conference opening
Dr Danijela Gnjidic, ASCEPT President
Assoc Prof Joseph Nicolazzo, APSA President
Dr Dan Wright, ASCEPT Co-chair
Dr Jonathan Penm, APSA Co-chair

Opening keynote presentation
Chair: Prof Kevin Pfleger, The University of Western Australia
Molecular phenomic and systems medicine approaches to healthcare in a COVID-19 dominated world - 100
Prof Jeremy Nicholson, Murdoch University, Perth

12.48 – 1.08  Concurrent session
Meet the speaker discussion group with Prof Jeremy Nicholson
Facilitator: Prof Kevin Pfleger, The University of Western Australia
(20 pre-registered participants)

1.08 – 1.14  Mini break

1.15 – 2.15  Concurrent symposium sessions

<table>
<thead>
<tr>
<th>Symposium 1: Communicating science in an age of uncertainty</th>
<th>Symposium 2: Peptide therapeutics</th>
<th>Symposium 3: Novel approaches to solving the antibacterial resistance crisis: TB and Malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair: Dr Ian Musgrave, University of Adelaide</td>
<td>Chairs: Prof Ross Bathgate, Florey Institute of Neuroscience and Mental Health, and Dr Martina Kocan, The University of Melbourne</td>
<td>Chair: Assoc Prof Lisa Kaminskas, The University of Queensland</td>
</tr>
<tr>
<td>Frankenfood and factory farms: Lessons from communicating science in agriculture - 101</td>
<td>Structure and dynamics of class B1 G protein-coupled receptors - 105</td>
<td>Rational design of ‘resistance resistant’ anti-tuberculosis drugs - 109</td>
</tr>
<tr>
<td>Dr Heather Bray, University of Western Australia</td>
<td>Prof Patrick Sexton, Monash University</td>
<td>Assoc Prof David Ascher, Baker Institute/ Bio21</td>
</tr>
<tr>
<td>Communicating science in an age of uncertainty: The foam and the fury – PFAS and possible risk of cancer - 102</td>
<td>Discovery and development of novel amylin agonists for obesity and diabetes - 106</td>
<td>Therapeutic drug monitoring in tuberculosis - 110</td>
</tr>
<tr>
<td>Prof Nicholas Buckley, The University of Sydney</td>
<td>Prof Debbie Hay, University of Auckland, New Zealand</td>
<td>Prof Jan-Willem C. Alffenaar, The University of Sydney</td>
</tr>
<tr>
<td>Communicating vaccine risk in the age of COVID-19, lessons from communicating toxicological fears to vaccine refusers - 103</td>
<td>Fluorescence imaging of peripheral nerves by a NaV1.7-targeted inhibitory cystine knot peptide - 107</td>
<td>Bromodomain proteins as potential malaria drug targets - 111</td>
</tr>
<tr>
<td>Dr Ian Musgrave, University of Adelaide</td>
<td>Assoc Prof Christina Schroeder, National Cancer Institute, USA</td>
<td>Dr Michael Duffy, Melbourne University</td>
</tr>
<tr>
<td>Communicating quality use of medicines during COVID-19 - 104</td>
<td>Unique mechanisms of GPCR biased signalling by peptidomimetic agonists of the relaxin receptor RXFP1 - 108</td>
<td>Panel discussion</td>
</tr>
<tr>
<td>Assoc Prof Darren Roberts, University of New South Wales</td>
<td>Prof Ross Bathgate, Florey Institute of Neuroscience and Mental Health</td>
<td></td>
</tr>
</tbody>
</table>

2.15 – 2.29  Coffee break

Tuesday 24 November 2020 program continued over page
Tuesday 24 November 2020 continued

2.30 – 3.50 Concurrent oral sessions

<table>
<thead>
<tr>
<th>Oral presentations 1: Education</th>
<th>Oral presentations 2: Oncology</th>
<th>Oral presentations 3: Toxicology and medicines-related harm</th>
<th>Oral presentations 4: Drug Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair: Dr Sarra El-Den, The University of Sydney</td>
<td>Chair: Dr Anna-Marie Babey, University of New England</td>
<td>Chair: Dr Rachael Farrington, The University of Adelaide</td>
<td>Chair: Dr Katie Leach and Dr Laureen May, Monash University</td>
</tr>
<tr>
<td>Interprofessional student-led Influenza Vaccination Clinic - 112</td>
<td>Effect of phenethylisothiocyanate on human breast cancer cells MDA-MB-231 and MCF-7 - 117</td>
<td>Exploring the TRAIL of doxorubicin-induced cardiotoxicity - 122</td>
<td>Characterising G protein coupling of angiotensin II and bradykinin receptor heteromers using mini G proteins - 127</td>
</tr>
<tr>
<td>Prof Jane Hanrahan, The University of Sydney</td>
<td>Dr Suong Ngo, The University of Adelaide</td>
<td>Ms Michelle Sims, University of Adelaide</td>
<td>Dr Elizabeth Johnstone, Harry Perkins Institute of Medical Research</td>
</tr>
<tr>
<td>Learning on the run – Pharmacy educators’ experiences with the Australian Pharmacy Residency Program - 113</td>
<td>Androgen regulated UDP-glucuronosyltransferases (UGT) 2B11 and 2B28 are prognostic indicators in luminal androgen receptor positive/molecular apocrine breast cancer - 118</td>
<td>The prevalence of medication-related hospital admissions in Australia: A systematic review and meta-analysis - 123</td>
<td>A new pertussis toxin-like protein complex as a tool for investigation of GPCR-Gα11 and Gζ3 signalling - 128</td>
</tr>
<tr>
<td>Mr Chih Yuan (Jason) Wang, The University of Queensland</td>
<td>Assoc Prof Robyn Meech, Flinders University</td>
<td>Miss Isabelle Gillooly, The University of Sydney</td>
<td>Mr Alastair Keen, Monash University</td>
</tr>
<tr>
<td>How do consumers interact with pharmacy students in educational settings? A systematic review - 114</td>
<td>A preliminary study on the anti-melanoma effect of novel resveratrol nanoparticle formulations - 119</td>
<td>National suicide prevention strategies by reducing access to poisons: A systematic review - 124</td>
<td>Differential G protein activation kinetics may underpin the beneficial aspects of clinically trialled adenosine A1 receptor atypical agonists - 129</td>
</tr>
<tr>
<td>Mr William Nguyen, The University of Sydney</td>
<td>Dr Yan Jing Yee, Curtin University</td>
<td>Miss Jessy Lim, The University of Sydney</td>
<td>Ms Samantha McNeill, Monash University</td>
</tr>
<tr>
<td>Preparation for practice – Implementation of an eBootcamp interactive prescribing series of workshops for final year medical students - 115</td>
<td>Triple negative breast cancer: Screening for the invasion amplifying CAMP-calcium feedforward loop mechanism - 120</td>
<td>Harm from cardiovascular medications: The omitted ‘C’ - 125</td>
<td>The structural basis for the UDP-sugar selectivity of human UDP-glycosyltransferase 2B7 (UGT2B7): A combined computational and experimental approach - 130</td>
</tr>
<tr>
<td>Assoc Prof Kellie Charles, The University of Sydney</td>
<td>MrTerrance Lam, Monash University</td>
<td>Miss Chariclia Paradissis, The University of Sydney</td>
<td>Dr Pramod Nair, Flinders University</td>
</tr>
<tr>
<td>Can multiple choice questions examine application of knowledge in online assessments? - 116</td>
<td>The role of UGT enzymes as novel modulators of lipid biosynthesis and SREBP signalling in breast cancer - 121</td>
<td>The prevalence and characteristics of psychotrophic-related hospitalisations in older people: A systematic review and meta-analysis - 126</td>
<td>Characterisation of the G protein coupling profiles of PAC1 receptor splice isoforms - 131</td>
</tr>
<tr>
<td>Dr Suong Ngo, The University of Adelaide</td>
<td>Mr Jai Meyers, Flinders University</td>
<td>Ms Ilsa Wojt, The University of Sydney</td>
<td>Miss Jessica Lu, Monash University</td>
</tr>
</tbody>
</table>

3.50 – 3.59 Mini break

4.00 – 4.30 British Pharmacological Society keynote presentation

Chair: Dr Danijela Gnjidic, The University of Sydney

The use of AI to enhance the success and efficiency of drug discovery and development - 132

Prof Jackie Hunter, Board Director, BenevolentAI, UK

4.31 – 5.15 Concurrent session

Meet the speaker discussion group with Jackie Hunter

Facilitator: Dr Danijela Gnjidic, The University of Sydney

(20 pre-registered participants)

4.31 – 4.51pm only

It’s rarely black and white - developing tolerance of uncertainty in our students

Assoc Prof Elizabeth Davis

(20 pre-registered participants)

Asking the hard questions - what are we doing to make diversity and inclusion matter?

Assoc Prof Tina Hinton

(20 pre-registered participants)

Get social - how social media can help maximise the reach and impact of our research

Dr Arisbel Batista Gondin

(20 pre-registered participants)

Networking event—‘speed dating’ style from 4.31 – 5.01pm

Time to view posters and visit the sponsors portal
### Wednesday 25 November 2020 | 12.00 – 6.00 pm Australian Eastern Daylight Time (AEDT)

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.00 – 11.00</td>
<td>The 54th Annual General Meeting of ASCEPT</td>
<td>Via zoom - please contact ASCEPT Executive Officer Katie Roberson at <a href="mailto:ascept@ascept.org">ascept@ascept.org</a> for zoom link.</td>
</tr>
<tr>
<td>11.00 – 12.00</td>
<td>2020 APSA Annual General Meeting</td>
<td>Zoom meeting link has been emailed to APSA members. Enquiries: <a href="mailto:apsa.general@outlook.com">apsa.general@outlook.com</a>.</td>
</tr>
<tr>
<td>9.00 – 11.59</td>
<td>Time to view posters and visit the sponsors portal</td>
<td>Sponsored by AFT Pharmaceuticals. Working to improve your health.</td>
</tr>
<tr>
<td>12.00 – 12.42</td>
<td>Concurrent session</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ASCEPT Early Achievement Award for Women</strong></td>
<td>Chair: Dr Danijela Gnijdic, The University of Sydney</td>
</tr>
<tr>
<td></td>
<td>Plant with the scorpion sting: Pharmacology of Australia’s most venomous plant “Gympie-Gympie” - 200</td>
<td>Chair: Dr Jennifer Deuis, The University of Queensland</td>
</tr>
<tr>
<td></td>
<td><strong>ASCEPT Gillian Shenfield Early Educator Award</strong></td>
<td>Chair: Assoc Prof Elizabeth Davis, Monash University</td>
</tr>
<tr>
<td></td>
<td>An adaptive e-tutorial for development of critical appraisal skills - 201</td>
<td>Dr Eryn Werry, The University of Sydney</td>
</tr>
<tr>
<td>12.45 – 2.20</td>
<td>Concurrent oral sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ASCEPT Garth McQueen student oral prize</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral presentations 5: Clinical Pharmacology</td>
<td>Sponsored by PKPDRX.</td>
</tr>
<tr>
<td></td>
<td>Oral presentations 6: Respiratory and Cardiovascular Pharmacology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral presentations 7: Pharmacy Practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Biased negative allosteric modulators for the calcium-sensing receptor have differential bronchodilator and bronchodilator effects in mouse precision cut lung slices</strong> - 203</td>
<td>Chair: Dr David Liew, Austin Health</td>
</tr>
<tr>
<td></td>
<td>Miss Jayin Diao, Monash University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Predictive performance of population pharmacokinetic models for tacrolimus in lung transplant recipients - 205</td>
<td>Chair: Assoc Prof Stavros Selemidis, RMIT University, and Mr Charlie Cohen, Baker Heart and Diabetes Institute</td>
</tr>
<tr>
<td></td>
<td>Ms Rani Singh, University of New South Wales</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apocynin ameliorates cigarette smoking-induced loss of skeletal muscle mass and function by preserving protein synthesis signalling - 215</td>
<td>Chair: Assoc Prof Stavros Selemidis, RMIT University, and Mr Charlie Cohen, Baker Heart and Diabetes Institute</td>
</tr>
<tr>
<td></td>
<td>Dr Stanley Chan, RMIT University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effects of ABC transporter modulation on olanzapine entry into the developing brain - 204</td>
<td>Chair: Dr Sara McMillan, Griffith University</td>
</tr>
<tr>
<td></td>
<td>Miss Yifan Huang, The University of Melbourne</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intracellular enzymatic activation of 4-hydroxyxoclophosphamide in leukocytes - 210</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mr Minghan Yong, University of Auckland</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spatial reference memory impairment is augmented in hypertensive mice following stroke - 216</td>
<td>Mr Abdallah Derbalah, University of Otago</td>
</tr>
<tr>
<td></td>
<td>Dr David Wong Zhang, La Trobe University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The influence of haemostatic system maturation on the dose-response relationship of unfractionated heparin - 211</td>
<td>Mr Abdallah Derbalah, University of Otago</td>
</tr>
<tr>
<td></td>
<td>Dr Maggie Lam, Monash University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relaxin inhibits matrix remodelling of collagen gels by asthmatic fibroblasts - 217</td>
<td>Mr Abdallah Derbalah, University of Otago</td>
</tr>
<tr>
<td></td>
<td>Dr Maggie Lam, Monash University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Expanding primary health care pharmacy practice in Aotearoa New Zealand: Testing theories using a realist-informed approach - 223</td>
<td>Dr Caroline Morris, University of Otago</td>
</tr>
<tr>
<td></td>
<td>Ms Deanna Mill, University of Western Australia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do pharmacy practice standards effectively describe behaviour? Reviewing practice standards using a behavioural specificity framework. - 222</td>
<td>Mrs Karlee Johnston, Australian National University</td>
</tr>
<tr>
<td></td>
<td>Ms Deanna Mill, University of Western Australia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking does not worsen skeletal muscle contractile function or loss caused by acute viral infection in mice - 206</td>
<td>Mr Kevin Mou, RMIT University</td>
</tr>
<tr>
<td></td>
<td>Towards precision dosing of vancomycin in critically ill patients: Evaluating predictive performance of pharmacometric models in Intensive Care Unit patients - 212</td>
<td>Mr Kevin Mou, RMIT University</td>
</tr>
<tr>
<td></td>
<td>Anandamide-induced vasodilatation in normotensive and hypertensive rats - 218</td>
<td>Mr Christopher Cunio, University of New South Wales</td>
</tr>
<tr>
<td></td>
<td>Interprofessional collaboration of general practice pharmacists in the Australian Capital Territory - 224</td>
<td>Mrs Thilini Sudeshika, University of Canberra</td>
</tr>
</tbody>
</table>
### Wednesday 25 November 2020 continued

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.20 – 2.49</td>
<td>Coffee break</td>
</tr>
<tr>
<td>2.50 – 3.20</td>
<td><strong>ASCEPT lecture</strong></td>
</tr>
<tr>
<td>Chair: Dr Daniela Grjic, The University of Sydney</td>
<td><strong>Translational studies in geriatric pharmacology: Contributing to the global challenge of ageing well</strong> - 227 Prof Sarah Hilmer, Royal North Shore Hospital; The University of Sydney</td>
</tr>
<tr>
<td>3.21 – 3.41</td>
<td><strong>Concurrent session</strong></td>
</tr>
<tr>
<td>Time to view posters and visit the sponsors portal</td>
<td>Meet the speaker discussion group with Prof Tina Brock (20 pre-registered participants)</td>
</tr>
<tr>
<td>3.41 – 3.49</td>
<td>Mini break</td>
</tr>
<tr>
<td>3.50 – 5.10</td>
<td><strong>Concurrent oral sessions</strong></td>
</tr>
<tr>
<td>Oral presentations 8: Pharmacoepidemiology—Drugs and ageing</td>
<td>Oral presentations 9: Neuro- &amp; Urogenital Pharmacology</td>
</tr>
<tr>
<td>Chair: Dr Lisa Kalisch Ellett, University of South Australia</td>
<td>Chair: Dr Jennifer Deuis, The University of Queensland</td>
</tr>
<tr>
<td>Outcomes of discontinuing anticholinergic medications in people living with dementia: A systematic review - 229 Dr Nagham Ailabouni, University of South Australia</td>
<td>Differential sleep/wake response and sex effects following acute suvorexant, MK-1064 and zolpidem administration in the rTg4510 mouse model of tauopathy - 234 Mr Ryan Keenan, The University of Melbourne</td>
</tr>
<tr>
<td>Utilising MedicineInsight to promote quality of care among Australians with dementia: A national general practice dataset - 230 Dr Edwin Tan, The University of Sydney</td>
<td>Effects of β-estradiol on porcine distal ureteral contractility - 235 Dr Iris Lim, Bond University</td>
</tr>
<tr>
<td>3.59 – 4.00</td>
<td><strong>ASCEPT lecture</strong></td>
</tr>
<tr>
<td>Chair: Dr Jennifer Deuis, The University of Queensland</td>
<td><strong>APSA lecture</strong></td>
</tr>
<tr>
<td>Giving/taking/matching/diversifying/translating/amplifying – Is collaboration worth it? - 228 Prof Tina Brock, Monash University</td>
<td>Chair: Assoc Prof Joseph Nicolazzo, Monash University</td>
</tr>
<tr>
<td>4.00 – 5.10</td>
<td><strong>Concurrent oral sessions</strong></td>
</tr>
<tr>
<td>Oral presentations 10: Drug Delivery, Disposition &amp; Response</td>
<td>Oral presentations 11: Improving patient outcomes</td>
</tr>
<tr>
<td>Chair: Assoc Prof Cornelia Landersdorfer, Monash University</td>
<td>Chair: Assoc Prof Joy Spark, University of New England</td>
</tr>
<tr>
<td>“The lesser of two evils”: Consumer perspectives on opioid deprescribing and the development of opioid deprescribing guidelines - 244 Ms Ali Langford, The University of Sydney</td>
<td>A safety, tolerability and pharmacokinetic study of a novel simvastatin silica-liquid hybrid formulation in healthy male participants - 239 Ms Tahlia Meola, University of South Australia</td>
</tr>
<tr>
<td>Outcomes of discontinuing anticholinergic medications in people living with dementia: A systematic review - 229 Dr Nagham Ailabouni, University of South Australia</td>
<td>Quantum dot nanomedicine formulations dramatically improve pharmacological properties and alter uptake pathways of metformin and nicotinamide mononucleotide in ageing mice - 240 Dr Nicholas Hunt, The University of Sydney</td>
</tr>
<tr>
<td>Utilising MedicineInsight to promote quality of care among Australians with dementia: A national general practice dataset - 230 Dr Edwin Tan, The University of Sydney</td>
<td>A meta-analysis on outcomes of medication misadventure among people with cognitive impairment or dementia - 245 Ms Anum Saqib Zaidi, University of Tasmania</td>
</tr>
</tbody>
</table>

---

*Wednesday 25 November program continued over page*
**Wednesday 25 November 2020 continued**

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older adult and caregiver attitudes towards deprescribing: A systematic review</td>
<td>Dr Kristie Weir, University of South Australia</td>
</tr>
<tr>
<td>Positive allosteric modulation of the M4 muscarinic acetylcholine receptor reverses MK-801 induced hyperlocomotion and sensorimotor gating deficits in mice</td>
<td>Dr Emma van der Westhuizen, Monash University</td>
</tr>
<tr>
<td>Piperacillin/tazobactam plus tobramycin versus Pseudomonas aeruginosa in two in vitro infection models</td>
<td>Miss Jessica Tait, Monash University</td>
</tr>
<tr>
<td>Development and validation of explicit criteria for identification of potentially inappropriate prescribing for people with type 2 diabetes mellitus</td>
<td>Mr Mohammed Ayalew, University of New England</td>
</tr>
<tr>
<td>Improving acute care for people with dementia: Dementia Cohort in Acute care RE settings study (D-CARE)</td>
<td>Dr Mouna Sawan, The University of Sydney</td>
</tr>
<tr>
<td>Utilizing mini-G protein biosensors and BRET to profile orexin receptor pharmacology</td>
<td>Miss Natasha Dale, Harry Perkins Institute of Medical Research</td>
</tr>
<tr>
<td>The effect of caffeine intake on the renal clearance of calcium, sodium and creatinine in healthy adults</td>
<td>Dr Hayley Schultz, University of South Australia</td>
</tr>
<tr>
<td>Duration of postoperative opioid use after hip or knee surgery: A systematic review and meta-analysis</td>
<td>Miss Xinyi Wang, The University of Sydney</td>
</tr>
<tr>
<td>Tools to evaluate medication management for caregivers of people with dementia: A systematic review</td>
<td>Miss Melissa Gench, The University of Sydney</td>
</tr>
<tr>
<td>Entry of valproate and lamotrigine into the developing brain</td>
<td>Mr Samuel Toll, The University of Melbourne</td>
</tr>
<tr>
<td>The effect of chronic polypharmacy and monotherapy on drug pharmacokinetics in mice</td>
<td>Dr John Mach, The University of Sydney</td>
</tr>
<tr>
<td>Supporting medication adherence in the Maori and Pacific Islander Community with Type 2 Diabetes in Australia</td>
<td>Mrs Natasha Taufatofua, The University of Queensland</td>
</tr>
</tbody>
</table>

5.10 – 5.14 Mini break

5.15 – 6.00 Concurrent session

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>It’s rarely black and white - developing tolerance of uncertainty in our students</td>
<td>Assoc Prof Elizabeth Davis (limited to 20 pre-registered participants)</td>
</tr>
<tr>
<td>Asking the hard questions - what are we doing to make diversity and inclusion matter?</td>
<td>Assoc Prof Tina Hinton (limited to 20 pre-registered participants)</td>
</tr>
<tr>
<td>Get social - how social media can help maximise the reach and impact of our research</td>
<td>Dr Arisbel Batista Gondin (limited to 20 pre-registered participants)</td>
</tr>
<tr>
<td>Networking event—‘speed dating’ style from 5.15 – 5.45pm</td>
<td>Time to view posters and visit the sponsors portal</td>
</tr>
</tbody>
</table>

5.45 – 6.30 Mini break

6.30 – 8.00 Poster session

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tools to evaluate medication management for caregivers of people with dementia: A systematic review</td>
<td>Miss Melissa Gench, The University of Sydney</td>
</tr>
<tr>
<td>Entry of valproate and lamotrigine into the developing brain</td>
<td>Mr Samuel Toll, The University of Melbourne</td>
</tr>
<tr>
<td>The effect of chronic polypharmacy and monotherapy on drug pharmacokinetics in mice</td>
<td>Dr John Mach, The University of Sydney</td>
</tr>
<tr>
<td>Supporting medication adherence in the Maori and Pacific Islander Community with Type 2 Diabetes in Australia</td>
<td>Mrs Natasha Taufatofua, The University of Queensland</td>
</tr>
</tbody>
</table>
**Thursday 26 November 2020, 12.00 – 4.00 pm**
Australian Eastern Daylight Time (AEDT)

### 9.00 – 11.59
Time to view posters and visit the sponsors portal

### 12.00 – 1.25
Concurrent session

**Certara New investigator award**

<table>
<thead>
<tr>
<th>Chair: Dr Danijela Gnijdic, The University of Sydney</th>
<th><strong>APSA Emerging Leaders session</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding the imprecision of precision dosing - 300</td>
<td>Implementation and evaluation of a virtual pharmacy Objective Structured Clinical Examination (OSCE) - 304</td>
</tr>
<tr>
<td>Dr Sophie Stocker, The University of Sydney</td>
<td>Dr Vivienne Mak, Monash University</td>
</tr>
</tbody>
</table>

**Novel BRET approaches to understand the complexities of endogenous GPCR function - 301**

<table>
<thead>
<tr>
<th>Dr Carl White, University of Western Australia</th>
<th>Pharmacist-led intervention using a web-based tool to reduce high-risk medication use in older in-patients - 305</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Stephanie Reuter Lange, University of South Australia</td>
<td>Dr Emily Reeve, University of South Australia</td>
</tr>
</tbody>
</table>

**Rational design of dose individualisation strategies for 5-Fluorouracil (5-FU) - 302**

<table>
<thead>
<tr>
<th>Dr Ashley Hopkins, Flinders University</th>
<th>Understanding the mechanisms behind the oral bioavailability enhancement of abiraterone acetate by silica-lipid hybrid formulations - 306</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dr Hayley Schultz, University of South Australia</td>
</tr>
</tbody>
</table>

**Concomitant proton pump inhibitor use and survival in patients with advanced cancer treated with atezolizumab - 303**

<table>
<thead>
<tr>
<th>Dr Christopher Langmead, Research Centre, Ireland</th>
<th>Evaluation of a pilot vancomycin therapeutic drug monitoring (TDM) service using an interrupted time series analysis - 307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Stephen Godson, The University of Sydney</td>
<td>Dr Sophie Stocker, The University of Sydney</td>
</tr>
</tbody>
</table>

### 1.25 – 1.39
Coffee break

### 1.40 – 2.40
Concurrent symposium session

**Symposium 4: Global challenges in education: Creating an inclusive environment**

<table>
<thead>
<tr>
<th>Chairs: Assoc Prof Elizabeth Davis, Monash University, and Assoc Prof Christian Moro, Bond University</th>
<th><strong>Symposium 5: Innovative therapeutic approaches of resolution pharmacology</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supporting and including our International students - 308</td>
<td>Chairs: Dr Chengxue Helena Qin, Monash University, and Prof Ross Vlahos, RMIT University</td>
</tr>
<tr>
<td>Assoc Prof Betty Exintaris, Dr Nilushi Karunaratne and Dr Suzanne Caliph, Monash University</td>
<td>Dysregulated ALX/FPR2 ligand expression defines a novel molecular subtype of lung cancer - 312</td>
</tr>
<tr>
<td>Promoting gender equity and diversity in the classroom - 309</td>
<td>Prof Steven Bozinovski, RMIT University</td>
</tr>
<tr>
<td>Assoc Prof Tina Hinton, The University of Sydney</td>
<td>Geographical and intra-facility variation in medicines use in Australian aged care facilities - 316</td>
</tr>
<tr>
<td>You wouldn’t ask a goldfish to climb a tree! Neurodiversity and associated opportunities for inclusion and improved outcomes for all - 310</td>
<td>Dr Janet Sluggett, University of South Australia</td>
</tr>
<tr>
<td>Dr Arlene Taylor, intégré Futures</td>
<td>Lipoxin, a novel approach to treat diabetes-associated atherosclerosis - 313</td>
</tr>
<tr>
<td></td>
<td>Prof Catherine Godson, Diabetes Complications Research Centre, Ireland</td>
</tr>
<tr>
<td>Strengthening Indigenous health workforces - 311</td>
<td>Advances in specialized pro-resolving mediator (SPM) G protein-coupled receptors - 314</td>
</tr>
<tr>
<td>Assoc Prof Karen Adams, Monash University</td>
<td>Dr Christopher Langmead, Monash University</td>
</tr>
<tr>
<td>Panel discussion</td>
<td>Medication Advisory Committees: A means to address unexplained variation in medicines use - 318</td>
</tr>
<tr>
<td></td>
<td>Prof Simon Bell, Monash University</td>
</tr>
<tr>
<td></td>
<td>The Registry of Senior Australians (ROSA) Outcome Monitoring System: Quality and safety indicators for examining unwarranted care variation - 319</td>
</tr>
<tr>
<td></td>
<td>Assoc Prof Gillian Caughey, South Australian Health and Medical Research Institute (SAHMRI)</td>
</tr>
</tbody>
</table>

### 2.40 – 2.59
Coffee break

*Thursday 26 November program continued over page*
Thursday 26 November 2020 *continued*

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Chair</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.00 – 3.33</td>
<td>APSA medal</td>
<td>Chair: Assoc Prof Joseph Nicolazzo, Monash University</td>
<td>Prof Andrew McLachlan, The University of Sydney</td>
</tr>
<tr>
<td></td>
<td>A Tribute to Dot Saville</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prof Kevin Batty, Curtin University</td>
</tr>
<tr>
<td>3.35 – 4.00</td>
<td>Meeting close and awards</td>
<td>Dr Danijela Gnjidic, ASCEPT President</td>
<td>Assoc Prof Joseph Nicolazzo, APSA President</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assoc Prof Joseph Nicolazzo, APSA President</td>
<td></td>
</tr>
</tbody>
</table>

*LiPhe: Leadership in pharmacy/pharmacology education - 320*
Poster abstracts

400
Raising awareness and early detection of undiagnosed atrial fibrillation through a systematic population-based screening program in Tasmania

Ibrahim J Abubakar1, Luke Bereznicki1, Barbara C Wimmer1, Corinna Dwan1, Woldesellassie M Bezahe1, Gregory M Peterson1. School of Pharmacy and Pharmacology, College of Health and Medicine, University of Tasmania, TAS, Hobart, Australia.

Introduction. Atrial fibrillation (AF) is a significant contributor to stroke and can be asymptomatic. Systematic population-based screening can promote AF awareness and identify people with undiagnosed AF in the community. However, information on systematic population-based screening for AF is lacking in Australia.

Aims. To assess the prevalence of previously undiagnosed AF and to promote AF awareness in Tasmania.

Methods. People aged ≥65 years with no history of AF were recruited through community events and media advertisements. Screening sessions for previously undiagnosed AF were conducted using the Microlife WatchBP Home-A blood pressure monitor at public events, health expos, shopping centres and clubs across Tasmania. Participants with positive screening results were referred to their general practitioners to confirm the presence of AF. These participants were followed up to determine the outcomes of the screening. At the screening venues, AF educational campaigns such as health talks and distribution of AF resource materials were provided to the public.

Results. A total of 1,704 eligible participants were screened at 79 sessions across Tasmania. Of these, 50 (2.9%) had a positive screening result. After a follow-up of these participants, the presence of AF was investigated in 47 (94%), and the device correctly identified AF in 22 (46.8%) and produced 25 (53.2%) false-positive results. Among those with confirmed AF, 6 (27.3%) had a history of AF but were not aware of the diagnosis, and 16 (72.7%) were identified to have previously undiagnosed AF, with a prevalence of 0.9% (95% CI, 0.58 to 1.52). Oral anticoagulation therapy (OAC) was initiated in 12 (87.5%) of those with a CHA2DS2-VASc score of ≥2. Also, 50% of all the participants became aware of AF through participation in the screening program and educational campaign.

Conclusion. A systematic population-based screening for AF identified 0.9% of older people (≥65 years) with previously undiagnosed AF in Tasmania. Although the performance of the Microlife WatchBP Home-A device was suboptimal under the study conditions, our findings indicate the possible benefits of systematic population-based screening and awareness raising for AF in the community.

401
Correlating functional studies of human bitter taste receptors (T2Rs) in humans and mice.

Conor J Bloxham1, Alexander Dashwood2, Elizabeth Cheesman2, Yusuke Yoshikawa1, Jake Russell1, Simon Foster1, Melissa E Reichelt1, Peter Molenaar2, Walter G Thomas. School of Biomed Sc, Univ of Queensland1, Brisbane, QLD. School of Biomed Sc, Queensland Univ of Tech2, Brisbane, QLD.

Introduction. We have reported the expression of T2Rs in the heart – activation of these receptors with picrotoxinin (a ligand for T2R46) in explanted human atrial trabeculae causes decreased contractility. Highly penetrant polymorphisms in T2R46 are non-functional in cell-based assays, but such a functional association in explanted cardiac tissue remains to be confirmed (Figure 1). As a corollary, we are also developing a humanised mouse model, where adeno-associated viruses deliver human T2R46 to cardiomyocytes in vivo. The lack of homology between rodent and human T2Rs provides a unique opportunity unambiguously determine the role of human T2Rs and polymorphisms within the heart.

Methods. Explanted right atrial appendages were obtained from patients at the Prince Charles Hospital. Dissected trabeculae were mounted and electrically paced before ligand-mediated changes in tissue contractility were recorded in response to picrotoxinin (1 mmol/L final). Hearts were isolated from mice injected with a cardiac-specific adeno-associated virus construct that expresses both a T2R and eGFP, and perfused in the Langendorff model. Cardiac parameters were recorded during infusion of increasing concentrations of picrotoxinin.

Results. In human cardiac tissue, the addition of picrotoxinin resulted in diminished cardiac contractility (Figure 1) and there does not appear to be a strong association with established T2R46 SNPs. Control experiments indicate that picrotoxinin does not bind/activate mouse T2Rs and does not cause cardio-depression in uninfected, isolated mouse hearts. Testing virally expressed human receptors are the focus of current experiments.

Discussion. T2Rs are expressed within the cardiovascular system and are thought to play a role in regulating normal cardiovascular physiology i.e. contractility and vascular tone. Studying human receptors and their genetic variants requires the establishment of models that can unambiguously delineate their function.
402

Pharmacological plasma cell depletion with Bortezomib does not attenuate angiotensin II-induced hypertension.

Hericka B Figueiredo Galvão,1 Jordyn M Thomas,1 Quynh N Dinh,1 Henry Diep1, Christopher G Sobey1, Antony Vinh1, Grant R Drummond1. Dept of Phys, Anat & Microbiol, La Trobe Univ1, Bundoora, VIC.

Introduction. B cell-depletion is known to blunt experimental hypertension (Chan et al, 2015), which suggests that B cells play a significant role in elevations in blood pressure (BP). B cells can differentiate into antibody secreting cells (ASCs) such as plasmablasts and plasma cells (Drummond et al, 2019), however, whether antibody production is a primary role for B cells in hypertension remains unclear.

Aims. To determine the effect of pharmacological depletion of ASCs on experimental hypertension.

Methods. Ten week-old C57BL6/J mice were randomly assigned to receive either angiotensin II (0.7mg/kg/day; s.c.) or vehicle (0.5% NaCl, 0.1% acetic acid) via osmotic minipump for 28 days. To deplete ASCs, the proteasome inhibitor, bortezomib (0.75mg/kg) or its vehicle (0.1% DMSO) were administered (i.v.) 3 days prior to minipump insertion, and then twice weekly thereafter. Weekly BP measurements were recorded by tail-cuff plethysmography. After 28 days of treatment, ASC abundance was measured in spleen and bone marrow. All experiments were performed blinded to treatment groups.

Results. Bortezomib treatment reduced the frequency of splenic plasmablasts (CD138+hiSca-1+Blimp-1+B220-1), respectively, compared to vehicle-treated mice. Bone marrow plasma cells, but not plasmablasts, were also reduced by 75% (vehicle vs bortezomib: 0.008 ± 0.002% vs 0.002 ± 0.001%, n=9-11) in bortezomib-treated mice. However, bortezomib has no effect on angiotensin II induced hypertension (vehicle vs bortezomib: 172 ± 7 vs 182 ± 4 mmHg, n=9-11).

Discussion. Pharmacological depletion of ASC did not ameliorate angiotensin II-induced hypertension, which suggests B cells may act via an alternate mechanism to promote experimental hypertension.


403

The pro-resolving lipid mediator lipoxin A4 protects against inflammation in diabetic cardiomyopathy

Ting Fu1,2, Minh Deo1, Muthukumar Mohan4, Madura Bose3, Eoin Brennan5, Catherine Godson5, Phillip Kantharidis5, Rebecca H Ritchie2,3,4,5, Chengxue Qin1,2,3,4,5, 1Dept of P&T, Univ of Melbourne, VIC; 2Dept of DDB, 3Dept of Diabetes, Monash Univ, VIC; 4Baker IDI, VIC, Australia; 5UCD DCRC, Univ College Dublin, Dublin, Ireland.

Introduction. Failure to resolve inflammation may contribute to the progression of diabetic cardiomyopathy. We have previously demonstrated that the pro-resolving lipid mediator lipoxin A4 (LXA4) attenuates the development and progression of diabetes-induced atherosclerosis, but its impact on diabetic hearts has not been fully explored.

Aim. To test the hypothesis that LXA4 may reduce inflammation by promoting the resolution of inflammation in the diabetic heart, thus supporting the development of an LXA4 based therapy to improve the outcome for patients with diabetic heart diseases.

Methods. 6-week-old male ApoE-/- mice were followed for 16wks after streptozotocin (55mg/kg/day i.p. for 5 days)-induced diabetes or vehicle control. Mice were randomly allocated to receive either LXA4 (5μg/kg) or vehicle (0.02% ethanol) via i.p. injections twice/week for the final 6wks. At the end of the study, mice were culled with an overdose of Sodium Pentobarbital (100mg/kg), organs harvested for ex-vivo analysis.

Results. Diabetic mice displayed elevated HbA1c levels, retarded body weight gain, increased infiltration of macrophages in the myocardium and elevated expression of M1-like macrophage marker (Table). Interestingly, administration with LXA4 significantly decreased the expression of M1-macrophage maker ms100A9 and inflammatory marker mI-1αβ. The macrophages content was no longer evident in the diabetic mice treated with LXA4.

<table>
<thead>
<tr>
<th>Non-diabetic mice</th>
<th>Diabetic mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>LXA4</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>32.06±1.78 (n=17)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.55±0.58 (n=15)</td>
</tr>
<tr>
<td>Macrophage content (No./0.43mm²)</td>
<td>11.73±4.04 (n=13)</td>
</tr>
<tr>
<td>ms100A9 (fold increase)</td>
<td>1.00±1.92 (n=17)</td>
</tr>
<tr>
<td>mI-1αβ (fold increase)</td>
<td>1.00±0.95 (n=17)</td>
</tr>
</tbody>
</table>

**p<0.001, ****p<0.0001 vs non-diabetic + vehicle; *p<0.05 vs diabetic + vehicle, (2-way ANOVA, Fisher’s post-hoc for multiple comparisons).

Conclusion. LXA4 may reduce inflammation by promoting the resolution of inflammation in the diabetic heart, thus supporting the development of an LXA4 based therapy to improve the outcome for patients with diabetic heart diseases.
Rivaroxaban for people with stage 4 chronic kidney disease and atrial fibrillation

Andreea S Kelso¹, Karl R Winckel¹−² Dept of Pharmacy, Princess Alexandra Hospital¹, Brisbane, QLD, Australia; School of Pharmacy, University of Queensland², Brisbane, QLD, Australia.

Background. Patients with stage 4 Chronic Kidney Disease (CKD) and atrial fibrillation (AF) are at high risk of both stroke from their AF and bleeding from anticoagulation for stroke prevention.(Kimachi et al, 2017;Weir et al, 2020) Until recently rivaroxaban was contraindicated in Australia for patients with AF and stage 4 CKD (GFR 15-30ml/min). In June 2020 the Australian Product Information (PI) was amended to allow rivaroxaban use in these patients. Rivaroxaban has advantages over warfarin in this population due to slower decline in renal function, and no clear association with vascular calcification.(Coleman et al, 2019; Yao et al, 2017; Zhang et al, 2019) It is unclear what proportion of stage 4 CKD patients with AF at our hospital were prescribed anticoagulation of any form before the PI change. This is important because this indicates another opportunity to prevent strokes in this cohort.

Aims: To determine what proportion of patients with stage 4 CKD and AF were anticoagulated prior to the rivaroxaban PI change.

Method. A retrospective observational audit was conducted in a random sample of inpatients with AF and stage 4 CKD between June-December 2019, to determine what anticoagulation was prescribed.

Results. To date thirteen patients were audited. 12/13 were prescribed oral anticoagulation (7/13 warfarin, 4/13 apixaban 2.5mg twice daily, 0/13 rivaroxaban, 1/13 dabigatran 110mg twice daily).

Discussion. Our results indicate that patients with stage 4 CKD and AF were prescribed anticoagulation at a high rate before the rivaroxaban PI change. Results also suggest these patients are mostly prescribed either warfarin or apixaban. There is concern that apixaban 2.5mg twice daily is a less effective treatment dose for AF (Alexander et al, 2016). Switching these patients to rivaroxaban may help reduce the risks of warfarin related vascular calcification and renal disease progression and allow use of a more effective dose of anticoagulation compared to apixaban 2.5mg twice daily. Further studies are warranted to examine prescriber views/attitudes to rivaroxaban use in this high-risk patient group.


Anandamide-induced vasodilatation in normotensive and hypertensive rats

Daria Kornienko, Makhala M Khammy. Dept of Pharmacol, Univ of Melbourne, Parkville, VIC, Australia

Introduction. Anandamide, an endogenous agonist of cannabinoid CB¹ receptors and transient receptor potential vanilloid 1 (TRPV1) channels, can inhibit vasoconstriction and decrease blood pressure by modulating sympathetic and sensory neurotransmission. The effect of anandamide action on vascular tone in hypertension is unclear.

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

Methods. In anaesthetised rats (2% isoflurane mixed with O²; spontaneous inhalation via nose cone), intravital microscopy was used to investigate mesenteric arterial diameter. Anandamide concentration-response curves were generated in U46619-constricted (300 nmol/L) arteries in the absence and presence of i) the CGRP receptor antagonist, BIBN 4096 (1 µmol/L); ii) the fatty acid amide hydrolase (FAAH) inhibitor, UR8937 (100 nmol/L) to inhibit anandamide degradation; and iii) capsaicin (10 µmol/L) to desensitise sensory nerves. Similar experimental protocols were performed in isolated mesenteric arteries via wire myography.

Results. Anandamide caused concentration-dependent relaxation in arteries from both rat groups. Maximum relaxation (Rmax) was greater in WKY rats than in SHR (89±9 vs. 47±5%, n=7 and 6, respectively; P<0.05). UR8937 enhanced anandamide-mediated vasodilatation in SHR only (Rmax, 89±6%, n=5; P<0.05). Capsaicin abolished anandamide-induced relaxation in both groups (Rmax, 12±6 and 11±8%, respectively, n=5; P<0.05) while BIBN 4096 had no effect. In contrast, in vitro anandamide relaxed pre-constricted mesenteric arteries isolated from WKY rats and SHR with similar potency and efficacy (pEC⁵₀, 6.22±0.04 vs. 6.31±0.05, respectively) and UR8937 had no appreciable effect on anandamide-mediated relaxation. Capsaicin inhibited anandamide-mediated relaxation in vitro and its inhibitory effect was more marked in SHR than WKY rats (63-fold vs. 23-fold decrease in pEC⁵₀, respectively; P<0.05).

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

© Andreea S Kelso, Karl R Winckel, Daria Kornienko, Makhala M Khammy. 2020 • ASCEPT-APSA 2020 • Brisbane, Queensland, Australia, 3-5 December 2020 • www.ascept-apsa.com • www.ascept-apsa20.com

Anandamide-induced vasodilatation in normotensive and hypertensive rats

Daria Kornienko, Makhala M Khammy. Dept of Pharmacol, Univ of Melbourne, Parkville, VIC, Australia

404

405
**406**

**Pravastatin targeting of myometrial artery endothelium-dependent vasodilation in preeclampsia**

Nathan M Luque¹, Sandra Lowe³, Leo Leader⁵, Steve Horowitz³, Timothy V Murphy¹, Shaun L Sandow¹²; Department of Physiology, University of New South Wales¹, Sydney, NSW, Australia; Biomedical Science, University of the Sunshine Coast², QLD, Australia; School of Women’s and Children’s Health and Royal Hospital for Women¹, University of New South Wales, Sydney, NSW, Australia

Introduction: Preeclampsia (PE) causes significant maternal and fetal morbidity and mortality. Maternal vascular endothelial dysfunction contributes to PE resulting in systemic organ dysfunction. Effective therapies remain to be identified.

Aims: This study aims to investigate the effect of *in vitro* pravastatin on uterine microvascular endothelial function in PE.

Methods: Myometrial radial arterioles from caesarean-section normotensive (NT) and PE patients were incubated with pravastatin (2mM/6h) *in vitro*. Electron microscopy, immunohistochemistry and pressure myography with pharmacological intervention characterized vessel structure and function.

Results: Overall caveolae density/µm is reduced 24% from 5.5±0.1 in NT (n=4, P<0.05) to 4.2±0.01 (n=4, P<0.05) in PE vessels, a further 31% to 1.9±0.8 (n=4, P<0.05) in PE vessels following treatment with pravastatin. Confocal immunohistochemistry showed reduced caveolin-1 expression in PE arterioles relative to NT, expression being reduced further in PE vessels following treatment with pravastatin. Functionally, PE vessels exhibited decreased vasodilator NO and IKCa activity, relaxation being predominantly S and BKCa mediated. Pravastatin incubation restored endothelium-dependent relaxation in PE samples to NT levels (Figure), enhancing the NO and IK components of relaxation.

Discussion: This data suggests treatment of preeclamptic vessels with pravastatin can be associated with improved vessel function as well as modulation of caveolae form and distribution.

**407**

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

Margaret A Mouat¹²³, Kristy L Jackson⁴, James LJ Coleman¹³, Madeleine R Paterson⁴, Robert M Graham¹³, Geoff A Head⁶, Nicola J Smith¹²³. Molecular Cardiology and Biophysics Div, Victor Chang Cardiac Research Institute¹, Sydney, NSW, Australia; Department of Pharmacology, UNSW³, Sydney, NSW, Australia; St Vincent’s Clinical School, UNSW⁴, Sydney, NSW; Neuropharmacology Laboratory, Baker Heart and Diabetes Institute⁵, Melbourne, VIC, Australia.

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

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

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

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

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

Min et al. (2010) Biochem Bioph Res Co 393:55-60
**408**

**Psychometric properties of self-reported medication adherence tools in cardiovascular disease: a systematic review**

Henok G. Tegegn1,2, Stuart Wark1, Edouard Tursan D’Espaignet1, M. Joy Spark1. School of Rural Medicine, University of New England1, Armidale, NSW, Australia; Clinical Pharmacy, University of Gondar2, Gondar, Amhara, Ethiopia.

Introduction. Many self-reported medication adherence (SRMA) tools have been developed and validated in patients with cardiovascular disease (CVD); however, it is not known which SRMA tool is most suitable for measuring medication adherence in patients with CVD.

Aims. This review aimed to evaluate the psychometric properties of SRMA tools to measure medication adherence in adults with CVD.

Methods. An electronic search was conducted in nine databases including PubMed, MEDLINE, CINAHL, ProQuest Health and Medicine, Cochrane Library, PsychInfo, Scopus, Embase, and Web of Science. Studies that have reported at least one of the psychometric properties for a SRMA tool in patients with CVD were included. Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was employed for assessing the methodological quality of the studies.

Results. The review included 74 studies and identified 38 separate SRMA tools. These tools were classified into three groups based on their medication adherence domains; group-1 tools had items with information specific to the extent of adherence; group-2 tools had items dealing with reasons for non-adherence, and group-3 tools asked about both adherence domains. The Voils extent of non-adherence tool from group-1, MASES, MASES-R, and SEAMS tools from group-2, and ARMS from group-3, had the most robust psychometric properties in their group. The most frequently assessed tool was MMAS-8 from group-3 with good psychometric properties; however, there was moderate evidence of insufficient results in its internal consistency.

Discussion. No study has evaluated all nine psychometric properties in a single study. Tools including the Voils extent of non-adherence tool, ARMS, MASES, MASES-R, and SEAMS showed robust psychometric properties to measure medication adherence in adults with CVD. Researchers and health care providers need to carefully consider the type of adherence phase, and the comprehensiveness of the SRMA tools, in addition to the adequacy of their psychometric properties.

---

**409**

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

Anida Velagic1, Jasmin Chendi Li1, Chengxue Qin2, Mandy Li3, Sarah A Marshall5, Owen L Woodman1, John D Horowitz4, Barbara K Kemp-Harper2, Rebecca H Ritchie1-2. Depts of Drug Discovery Biology1, Pharmacology2 and Obstetrics and Gynaecology3, Monash Univ, Clayton, VIC; Queen Elizabeth Hospital, Univ of Adelaide, SA4.

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

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

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

<table>
<thead>
<tr>
<th>DEA/NO (10^{-5} M)</th>
<th>Angeli’s salt (10^{-5} M)</th>
<th>Insulin (33.3 IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND (n=8)</td>
<td>Diabetic (n=8)</td>
<td>ND (n=8)</td>
</tr>
<tr>
<td>ΔLVDP (mmHg)</td>
<td>5.7±0.7</td>
<td>2.3±0.6*</td>
</tr>
<tr>
<td>ΔLVEDP (mmHg)</td>
<td>2.6±0.6</td>
<td>1.1±0.2*</td>
</tr>
<tr>
<td>ΔLV+dp/dt (mmHg/s)</td>
<td>147±19</td>
<td>96±18*</td>
</tr>
<tr>
<td>ΔLV-dp/dt (mmHg/s)</td>
<td>-133±8</td>
<td>-78±7*</td>
</tr>
<tr>
<td>ΔCoronary flow (mL/min)</td>
<td>7.0±0.7</td>
<td>4.6±0.9*</td>
</tr>
<tr>
<td>ΔHeart rate (bpm)</td>
<td>14.5±2.3</td>
<td>21.2±1.3*</td>
</tr>
</tbody>
</table>

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

Discussion. These findings demonstrate for the first time that the HNO donor Angeli’s salt circumvents NO• resistance in the diabetic insulin-resistant myocardium, highlighting the therapeutic potential of HNO donors to treat acute diabetes-associated impairments in cardiac function.
Spatial reference memory impairment is augmented in hypertensive mice following stroke

David E. Wong Zhang, Grant R. Drummond, Christopher G. Sobey & T. Michael De Silva. Department of Physiology, Anatomy and Microbiology, La Trobe University, Melbourne, VIC, Australia.

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

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

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

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

Efficacy and safety of metaraminol infusions in critical care: A systematic review and meta-analysis

Arwa A Sardaneh1,2, Sujita Narayan1, Jonathan Penn1, Matthew Oliver2, David Gattas2, Andrew J McLachlan1, Asad E Patanwala1,2. School of Pharmacy, Univ of Sydney,1 Sydney, NSW; Royal Prince Alfred Hospital,2 Sydney, NSW.

Introduction. Noradrenaline is the preferred first-line vasopressor according to guidelines in the treatment of shock in critical care. However, there has been increasing use of metaraminol infusions as a first-line agent in Australasia and Europe in rates up to 42%. The lack of guidance of metaraminol use in published guidelines has not limited its use in the critical care population.

Aims. To assess the efficacy and safety of metaraminol infusions in comparison to other vasopressors in critically ill patients with shock with regard to hospital mortality, effect on haemodynamics (mean arterial pressure or systolic blood pressure), duration of vasopressor use, and adverse events.

Methods. A systematic review and meta-analysis of controlled trials and observational studies was conducted. Eight electronic databases and nine trial registers were searched from inception to 18 August 2020.

Results. Out of 1387 eligible articles, three observational studies and one controlled trial were included involving a total of 54 patients. Study patients had different types of shock including septic (n=28), cardiogenic (n=21), hypovolemic (n=3) and neurogenic shock (n=2). All studies compared metaraminol to noradrenaline and were of low quality and high risk of bias. There was no difference in hospital mortality between metaraminol and noradrenaline groups (OR 0.68, 95% CI 0.15 to 3.09; p=0.62). There was no difference in the effect on blood pressure between metaraminol and noradrenaline (standardised mean difference 0.09, 95% CI -0.46 – 0.64; p=0.76). None of the studies reported the duration of vasopressor use or adverse drug events such as extravasation or tissue injury.

Discussion. There is limited and low-quality efficacy and safety data to support the use of metaraminol over other vasopressors in critically ill patients with shock.
**412**

The association between menopausal status and remission in rheumatoid arthritis patients receiving disease modifying antirheumatic drugs

Dala N Daraghmeh1, Ashley Hopkins2, Catherine King3, Ahmad Y Abuhelwa3, Michael D Wiese1. 1School of Pharmacy and Medical Sciences, University of South Australia2, Adelaide, SA, Australia. 2College of Medicine and Public Health, Flinders University, Bedford Park 5042, SA, Australia

Introduction. Rheumatoid arthritis (RA) is an auto-immune inflammatory disease and is more prevalent in females than males with a ratio of 4:1 at younger ages (<50 years old) and 2:1 at older ages (>60 years old). It has been suggested that alteration in the balance of sex hormones is associated with the development of RA.

Aims. To examine the association between baseline menopausal status and remission likelihood in RA patients treated with tocilizumab (TCZ) and/or conventional synthetic disease modifying antirheumatic drugs (csDMARDs).

Methods. Data were pooled from 5 phase III clinical trials where participants with RA were treated with TCZ and/or csDMARD. Available data included documented baseline menopausal status (pre vs post), age, sex hormone supplement use, weight, race, number of previous DMARDs and baseline disease scores. Remission criteria were set according to the simplified and clinical disease activity index (SDAI and CDAI respectively), and 28-joint disease activity score (DAS28). The association between menopausal status and the time of first remission was assessed via Cox proportional analysis.

Results. The analysis included data from a total of 4,473 female patients treated with TCZ and/or csDMARDs, of which 3028 (68%) were post-menopausal and 1,445 (32%) pre-menopausal and 232 (7.7%), 284 (19.7%) were using sex hormone supplements, respectively. In the pooled analysis, pre-menopausal status was associated with significantly higher SDAI remission compared to post-menopausal status on univariable (HR 1.21 [95%CI 1.08-1.36], P=0.002) and adjusted (HR 1.87 [1.004-3.48, P =0.04]) analysis. Similar associations were observed using CDAI and DAS28-ESR remission. Sex hormone use was associated with significantly higher SDAI remission on univariable (HR 1.26 [1.07-1.42, P=0.038]) and adjusted (HR 1.20 [1.01-1.42, P=0.05]) analysis. The association of female reproductive status and sex hormone use with remission were independent of the type of RA therapy (interaction P>0.05).

Conclusion. Premenopausal reproductive status and sex hormone use were independently associated with more frequent remission in female RA patients, regardless of the type of DMARDs used.

**413**

Chronic polypharmacy and increasing Drug Burden Index (DBI) impair cognitive function in aged mice

Gizem Gemikonakli1,2, John Mach1,2, Trang Tran1,2, Susan Howlett3, Rafael de Cabo4, David G Le Couteur2,5 & Sarah N Hilmer1,2.

Lab of Ageing and Pharmacology, Kolling Institute, Royal North Shore Hosp, Sydney, NSW, Australia 1. Northern Clinical School, Univ of Sydney, NSW, Australia 2. Dalhousie University, Halifax, Canada 3. Translational Gerontology Branch, National Institute on Aging, Maryland, USA 4. ANZAC Research Institute, Sydney, NSW, Australia 5.

Introduction. Ageing, polypharmacy (>5 medications) and increasing DBI (anticholinergic and sedative medication exposure) are associated with impaired cognitive function. Preclinical models can assess causation and mechanisms.

Aims. We investigated whether chronic polypharmacy or monotherapy, with increasing DBI and/or cessation (deprescribing), affected learning and/or memory in ageing mice.

Methods. 12-month-old male C57BL/6 mice received either control diet or study drug(s) at therapeutic doses. The three polypharmacy diets had zero DBI (metoprolol, simvastatin, omeprazole, paracetamol, irbesartan), low DBI (metoprolol, simvastatin, omeprazole, paracetamol, citalopram) and high DBI (metoprolol, simvastatin, citalopram, oxycodone, oxybutynin). Individual drugs from the high DBI regimen were tested as monotherapies. At 21-months, animals were randomly stratified to continue treatment or have it gradually deprescribed. Barnes Maze learning occurred over 4 days, with an introduction to the target hole before trial 1 (only day 1), followed by 4 trials (all 4 days), followed by short-term memory test (ST; day 5) and long-term memory test (LT; day 10) at 12-, 21- and 24-months.

Results. Preliminary analysis showed High-DBI polypharmacy mice (n=23-12; p<0.05) reduced time exploring the target hole at ST with a treatment-age interaction effect showing high-DBI decreased exploration time of target hole at ST and increased at LT with increasing age, compared to control (n=24-29; p<0.05). At 24-months high-DBI and low-DBI showed impaired learning with longer time and distance travelled before arriving at the target hole on day 1 trial 1, while deprescribed high-DBI (n=16) and low-DBI (n=17) performed similar to control.

Discussion. Drug treatment with polypharmacy regimens with DBI>0 increased learning time, and impaired short-term memory. Preclinical results suggest polypharmacy impacts cognition, and further analysis will explore the role of each monotherapy vs polypharmacy.
How are antibiotics prescribed for open reduction internal fixation procedures?

Sarah Hassan1,2, Juliette Gentle1,2, Vincent Chan1, Julie Stevens1, Ieva Stupans1. Pharmacy, School of Health and Biomedical Sciences, RMIT Univ1, Melbourne, VIC, Australia; Dept of Orthopaedics, Northern Health2, Melbourne, VIC, Australia

Introduction. Surgical antibiotic prophylaxis (SAP) is a common indication for antimicrobial use in Australia, however inappropriate use can contribute to antimicrobial resistance and increase costs. New SAP recommendations in the Therapeutic Guidelines (published April 2019) suggests the use of single dose prophylaxis for internal fixation.

Aim. The aim of this study was to determine how antibiotics are prescribed for patients undergoing open reduction internal fixation (ORIF) of upper and lower limbs at Northern Health following guideline update.

Methods. A retrospective audit was conducted for patients who underwent ORIF of closed fractures between July and December 2019. Medical records were reviewed for antibiotic choice, dose, route and time of administration and duration of prophylaxis.

Results. 209 patients were included in this study. Pre-operative antibiotic administration was documented in 96% of patients. Whilst cefazolin 2g was commonly administered pre-operatively as per guideline recommendations (94% of cases), the majority of patients (79%) received post-operative antibiotics. An extended duration of prophylaxis (>24 hours) was observed in 11% of cases.

Discussion. Variability exists as to whether antibiotics are administered post-operatively, with a need to determine the factors that contribute to an extended duration of prophylaxis. Our findings suggest that guideline amendment, in isolation, does not reflect a change in practice and further research is required to understand what influences prescribing in this setting.

Cultural Perceptions of Gout in East Asia

Maria A Hernandez Castellanos1,2, Ming-Han Lee2, Wu Yi Zheng3, Melissa T Baysari3, Eindra Aung1,2, Richard O Day1,2, Matthew J Coleshill1,2, Sophie L Stocker1,2. St. Vincent’s Hospital1, Sydney, NSW, Australia; St. Vincent’s Clinical School, Faculty of Medicine, UNSW2, Sydney, NSW, Australia; Faculty of Medicine and Health3, The University of Sydney, Sydney, NSW, Australia.

Introduction. Management of gout is suboptimal worldwide, including in East Asia. Cultural perceptions and ethnic-specific factors (e.g. Caucasian stigmatisation; Maori views of stoicism) have been shown to contribute to the poor management of gout in non-East Asian countries. As of yet, no studies have explored perceptions of gout in East Asia.

Aims. To investigate the perceptions of healthcare providers (HCPs) and patients with gout in East Asia to identify barriers to optimal gout management.

Methods. Participants included 8 HCPs and 2 patients with gout from East Asia (China, Taiwan, South Korea and Japan). Semi-structured interviews were conducted and transcribed verbatim. Transcripts were inductively analysed for themes. Data collection ceased once thematic saturation was reached.

Results. HCPs, particularly rheumatologists, reported that delayed or inadequate management of gout was the result of: 1) Patients often considering gout to be a minor illness that did not require medical attention; 2) Clinicians in primary care not being well educated on management strategies and only providing short-term symptomatic treatment. Selection of urate-lowering therapy was influenced by concerns of toxicity, specifically allopurinol hypersensitivity syndrome – a reaction more common in people of East Asian ancestry. Consequently, Taiwanese rheumatologists reported using benz bromarone or febuxostat as the first-line urate-lowering therapy. HCPs and patients alike perceived that there was no negative stigma or sense of shame associated with a diagnosis of gout. Patients also reported that gout was viewed as a minor illness and believed gout to be secondary to their pre-existing renal impairment.

Discussion. Unlike Western cultures, in East Asian communities gout is not associated with negative stigma; rather it is considered by patients to be a minor disease. This perception impedes optimal management and timely medical assistance. Treatment approaches selected by HCPs, particularly in Taiwan, were influenced by reported increased risk of toxicity to allopurinol and association to ethnic genetic predisposition.
Bayesian approach shows lack of difference between Aboriginal and Caucasian kidney transplant recipients in mycophenolic acid and tacrolimus pharmacokinetics

Nick Holford¹, David Metz², Katherine Barraclough². Pharmacology & Clinical Pharmacology, University of Auckland¹, Auckland, New Zealand; Nephrology, University of Melbourne², Melbourne, VIC, Australia.

Introduction. Aboriginal Australians experience worse patient and graft outcomes following kidney transplantation compared with Caucasian Australians.

Aim. To determine if immunosuppressant pharmacokinetics can explain outcome differences.

Methods. 32 Aboriginals and 14 Caucasians who were >3 months post-transplant and receiving mycophenolate mofetil and tacrolimus underwent a 4 sample PK study. Empirical Bayes estimates (EBEs) of mycophenolic acid (unbound) and tacrolimus (whole blood) clearance were obtained using previously developed PK models (Metz 2018, Storset 2014).

Results. For both drugs, there was negligible difference in median clearance and variability of clearance EBEs between Aboriginal and Caucasian kidney transplant recipients.

Discussion. The Bayesian method leveraged existing knowledge about PK of two immunosuppressants to ask a specific question about race-associated differences in PK. The lack of any evidence for a difference indicates that a target concentration intervention approach to dose individualization (NextDose www.nextdose.org) can use existing PK priors without consideration of Aboriginal race.


Development and validation of a Liquid Chromatography tandem Mass Spectrometry (LCMSMS) assay investigating pharmacokinetics (PK) of phosphatidylethanol.

Daniel White¹, Sean O’Halloran¹,², David A. Joyce¹,²,³, Gerard MacQuillan³, PathWest¹, Nedlands, WA, Australia; University of Western Australia², Crawley, WA; Sir Charles Gardiner Hospital³, Nedlands, WA, Australia.

Introduction. Phosphatidylethanol (PEth) has generated interest as a biomarker for ethanol consumption because it is uniquely formed, incorporated and accumulated in red cell membranes by the action of phospholipase D on membrane phosphatidylcholine with ethanol.

Aims. To develop and validate an LCMSMS assay and investigate PK of PEth by monitoring concentrations in saline-washed red cells from participants who keep contemporaneous diaries of ethanol intake.

Methods. PEth was extracted from saline-washed red cells with isopropanol and injected onto a Waters XEVO TQS triple quadrupole LCMSMS. International method validation guidelines were implemented.

Results. Method validation demonstrated linearity between LLOQ of 8ng/mL and ULOQ of 2093ng/mL of washed red cells, with satisfactory inaccuracy, imprecision and signal-to-noise for the LLOQ. Interday, intraday and instrument imprecision was less than 6% over three control concentrations with accuracy greater than 92.9%. Use of a deuterated PEth-d5 internal standard compensated for matrix effects.

Discussion. Ethics approval was obtained to recruit participants in three groups – A) teetotallers, B) drinkers keeping an ethanol diary, and C) drinkers consenting to abstain from ethanol for 4 weeks. Lack of any signal from Group A participants demonstrated specificity of the assay against false positives. Elimination profile from 3 participants in Group C is shown above – demonstrating approximate half-life of 7days with first order kinetics. Preliminary results from Group B demonstrate wide inter-individual PEth concentrations when evaluated against ethanol consumption suggesting need for further investigation of patient covariates for this marker.

Applications of using Drug Monitoring for Ivacaftor and Tezacaftor Treatment Response in Cystic Fibrosis

Felisa Reyes-Ortega¹, Fiona Qiu², Elena K. Schneider-Futschik²

Affiliations: ¹University Hospital Reina Sofia, Maimónides Biomedical Research Institute of Córdoba (IMIBIC); 14004 Córdoba, Spain; ²Department of Pharmacology & Therapeutics, The University of Melbourne, Parkville, VIC, 3010, Australia.

Background: Ivacaftor-tezacaftor is a new breakthrough cystic fibrosis (CF) drug combination that directly modulate the activity and trafficking of the defective CF transmembrane conductance regulator protein (CFTR) underlying the CF disease state. We report the first therapeutic drug monitoring assay for these drugs and their application in the clinic.

Methods: A rapid and precise novel method for the quantification of ivacaftor, its metabolites and tezacaftor in human plasma was developed and validated using multiple reaction monitoring mass spectrometry (MRM/MS).

Results: The MRM/MS analytical method was validated at a concentration range from 0.0025 µg/mL to 1 µg/mL for ivacaftor, ivacaftor-M1, ivacaftor-M6 and tezacaftor in human plasma. The method displayed good accuracy (90.62 - 94.51%) and reproducibility (99.91-100%) including at low concentrations 0.01 µg/mL. The reported method can accurately quantify ivacaftor, ivacaftor-M1, ivacaftor-M6 and tezacaftor at low concentrations in human plasma. The assay was successfully utilised in CF patients with severe liver impairment, pharmacokinetic/pharmacodynamic population analysis and quantification studies in animal models.

Conclusion: We have established a cost-efficient and timely method for measuring ivacaftor, its metabolites and tezacaftor in human plasma and tissue samples suitable for high-throughput applications in the hospital settings, clinical trials or in fundamental research.

A step forward in patient safety - understanding barriers to correct intravenous medication administrations

Catriona F J Shen¹,², Melissa T Baysari³, Ethan Watters⁴, Deborah Debono⁵, Richard O Day¹,², Jane E Carland¹,², Sophie L Stocker¹,² Clinical Pharmacology and Toxicology, St. Vincent's Hospital¹, Sydney, NSW, Australia; St. Vincent’s Clinical School, Faculty of Medicine, UNSW², Sydney, NSW, Australia; Faculty of Medicine and Health, The University of Sydney³, Sydney, NSW, Australia; St. Vincent’s Hospital⁴, Sydney, NSW, Australia; Centre for Health Services Management, School of Public Health, University of Technology Sydney⁵, Sydney, NSW, Australia.

Introduction. Medication and procedural errors occur in approximately 75% of intravenous (IV) drug administrations. Relatively few studies have explored nurses’ perspectives on factors contributing to, and strategies to prevent, errors.

Aims. To identify common medication and procedural IV errors reported to a voluntary incident reporting system and to explore nurses’ perspectives on the factors contributing to, and strategies to mitigate, IV errors.

Methods. IV drug administration incidents reported between January 2015 and May 2020 were reviewed. Medication and/or procedural errors were categorised using the Australian Commission on Safety and Quality in Healthcare’s medicine incident classification system. A snowballing approach was used to recruit nurses to participate in interviews about their views on IV medication errors. Emergent themes were identified from interview transcripts.

Results. Of all reported IV medication administration incidents (n=706) 86.1% and 37.2% contained at least one medication and procedural error, respectively. Wrong IV rate was the most frequent medication error type (29%), and failure in double checking and signing procedures the most frequently reported procedural error (19%). Nurses from critical care (n=9) and general wards (n=19) reported that (i) workarounds, developed as a result of time constraints and workload, (ii) lack of education/experience and access to appropriate resources and (iii) difficulties in interpreting policies and procedures, are all contributors to the occurrence of IV drug administration errors. Regular, proactive, case-based education was a commonly identified strategy to prevent IV errors. Development and revision of IV drug administration policies with nurse consultation and amendments to existing models of care to include team-based (e.g. paired) nursing allocations to better support increasing patient acuity were also reported as potential strategies.

Discussion. Delivery of practical training and education on IV infusion rates (e.g. smart pump use and rate calculations) along with improved access to resources (e.g. policies) are potential strategies to minimise wrong IV rate errors arising from lack of experience. Changes to models of care were also suggested to maintain patient safety and minimise errors related to high nurse workloads.
**420**

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

Rani M Singh¹,², Ranita Kirubakaran,¹,² Richard O Day¹,², Jane E Carland¹,², Sophie L Stocker¹,². Dept of Clin Pharmacol, St Vincent’s Hosp¹, Darlinghurst, NSW, Australia; St Vincent’s Clin School, Univ of NSW², Kensington, NSW, Australia.

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

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

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

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

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

**421**

**Adverse drug reactions presenting to acute medical admissions: a pilot prevalence study**

Jules Thompson, James Coulson. Cardiff University, Cardiff, GNS, Wales.

Introduction. Adverse drug reactions (ADRs), defined by the Edwards and Aronson (2000) definition, accounted for 6.5% of all unscheduled hospital admissions in a 2002 observational study in Liverpool and Merseyside. The authors estimated the projected cost to NHS England was £466 million and 72% of ADRs recorded were potentially avoidable. A retrospective study of ADR-related admissions, defined by ICD-10 code, to English hospitals between 1998 and 2005 reported an admission rate of 0.5%, suggesting under-reporting may be a significant factor in the difference with prospective observational studies.

Aims. To determine the incidence of ADR-related admissions in the University Hospital, Llandough, over a 3 week period, in order to estimate the point-prevalence of ADR-related acute admissions in Wales, compared with our historical coding rate of approximately 0.5%.

Methods. An observational-prospective service audit to describe the point-prevalence of ADR-related admissions to University Hospital Llandough Medical Emergency Assessment Unit over 3 weeks in March 2019. Anonymized participant data was collected from the paper case-notes of unscheduled admissions. ADRs were determined by a consultant-grade clinical pharmacologist.

Results. Thirty-four cases met the inclusion criteria. 32% of the admissions were caused by or contributed to by an ADR (95% confidence interval (CI) 0.17-0.51), compared with our historical coding rate of 0.5%, p = 0.01. 19% of admissions were directly caused by an ADR (CI 0.068 to 0.35).

Discussion. The prevalence of ADR-related hospital admissions in Llandough hospital was greater than that historically reported by clinical coding. Further, detailed, studies are warranted to improve the identification of ADR-related admissions as a step towards reducing their prevalence.
422
Application of physiologically-based pharmacokinetic modelling to understand real-world outcomes in patients receiving imatinib for chronic myeloid leukaemia
Josephine A. Touma1, Annette S. Gross1,2, Jeffry Adiwidjaja1, Andrew J. McLachlan1. Sydney Pharmacy School, The University of Sydney1, Sydney, NSW, CPMS, GlaxoSmithKline R&D2, Sydney, NSW.

Introduction. There is large variability in imatinib outcomes in the treatment of chronic myeloid leukaemia (CML). Many patients experience severe adverse drug reactions (ADRs) and some never achieve Early Molecular Response (EMR), an important predictor of achieving stable deep molecular response and therefore treatment-free remission.

Aim. To use physiologically-based pharmacokinetic (PBPK) modelling and simulation to predict imatinib steady-state (ss) exposure in patients with CML to investigate variability in outcomes observed.

Methods. A previously validated imatinib PBPK model (Simcyp Simulator v18, Certara) was used to predict imatinib AUC_{ss}, C_{min,ss} and C_{max,ss} for patients from a real-world retrospective observational study. Differences in imatinib exposure were evaluated in patients with different clinical outcomes, (1) EMR achievement (n=45) and (2) occurrence of grade ≥ 3 imatinib-related ADR (n=68), using the Kruskal-Wallis rank sum test. Sensitivity analyses explored the influence of patient characteristics and drug interactions on imatinib exposure.

Results. The patient cohort was 59% male, 74% European ancestry with a median age of 56 years. The majority (71%) had been prescribed at least 1 medication with the potential to interact with imatinib (52% CYP3A4 substrate, 8% CYP3A4 inhibitor, 6% P-gp inhibitor, 7% CYP2C8 inhibitor, 2% CYP3A4 inducer). Simulated imatinib exposure was significantly higher in patients who achieved EMR compared to patients who did not (geometric mean AUC_{ss}, gp inhibitor, 7% CYP2C8 inhibitor, 2% CYP3A4 inducer). Simulated imatinib exposure was significantly higher in patients who prescribed at least 1 medication with the potential to interact with imatinib (52% CYP3A4 substrate, 8% CYP3A4 inhibitor, 6% P-gp inhibitor, 7% CYP2C8 inhibitor, 2% CYP3A4 inducer). Simulated imatinib exposure was significantly higher in patients who achieved EMR compared to patients who did not (geometric mean AUC_{ss}, 51 vs. 43 µg*h/mL, P<0.05; C_{min,ss} 1.1 vs. 0.9 µg/mL, P<0.05; C_{max,ss} 3.4 vs. 2.8 µg/mL, P<0.05). Patients who experienced grade ≥ 3 ADR had a significantly higher simulated imatinib exposure compared to patients who did not (AUC_{ss} 56 vs. 46 µg*h/mL, P<0.05; C_{min,ss} 1.23 vs. 1.00 µg/mL, P<0.05; C_{max,ss} 3.73 vs. 2.96 µg/mL, P<0.05). The PBPK simulations identified a range of patient (sex, age, total body weight, abundance of hepatic CYP2C8 and CYP3A4, alpha-1-acid glycoprotein concentrations, liver and kidney function) and medication-related factors (dose, concomitantly administered CYP2C8 modulators) that could contribute to the inter-individual variability in imatinib plasma concentration.

Discussion. Relationships between imatinib plasma exposure, EMR achievement and occurrence of severe ADRs support the rationale for therapeutic drug monitoring to guide imatinib dosing to achieve optimal outcomes in CML patients.

423
VTE prophylaxis in orthopaedic surgery – Patient individualised or ‘one-dose-fits-all’?
Nameer van Oosterom1,2, Michael Barras3, Neil Cottrell2. Dept of Pharm, Princess Alexandra Hosp1, Brisbane, QLD, Australia; School of Pharm, Univ of Queensland3, Brisbane, QLD, Australia.

Introduction: Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are one of the highest risks factors for venous thromboembolism (VTE). Therefore, appropriate prophylaxis is imperative. Aspirin for VTE prophylaxis post-THA/TKA is controversial with differing recommendations in international guidelines. It is thought aspirin may not be appropriate for higher risk patients, including those at risk of aspirin resistance: the elderly (≥65 years), obese (body mass index (BMI) ≥30 mg/kg²), and those with diabetes mellitus or dyslipidaemia.

Aims: To investigate the influence of major risk factors on the selection of VTE prophylaxis after elective THA/TKA.

Methods: A retrospective multisite cohort study between October 2017 and September 2018 of six hospitals in Queensland, Australia. Analysis of VTE prophylaxis (aspirin, rivaroxaban and low-molecular weight heparins (LMWH)) with patient and surgical factors were conducted using Pearson’s chi-square.

Results: A total of 1,011 patients (43.1% THA, 56.9% TKA) were included with a mean (SD) BMI of 32.1 (±7.0) kg/m², age of 65.9 (±11.0) years and 43.6% males. Discharge prophylaxis was prescribed in 94.4% of patients where aspirin was the most common (42.1%). Compared to rivaroxaban, patients were less likely to be prescribed aspirin if they had diabetes (p=0.002) or age ≥65 (p<0.001). No other major risk factors for aspirin resistance were related to the drug prescribed for discharge VTE prophylaxis.

Discussion: Drug selection did not seem to be impacted by the presence of risk factors for aspirin resistance apart from diabetes and age ≥65 years. The uncertainty of aspirin’s efficacy in higher risk patients, in conjunction with its substantial use in patients at risk of resistance is of concern. Further research is required to investigate aspirin resistance post-THA/TKA and the clinical outcomes of resistance.
424

A common allosteric mechanism for stabilising agonist ligand binding at GPCRs

Wessel A. C. Burger1, Christopher J. Draper Joyce2, Arthur Christopoulos1, Celine Valant1, David M. Thal1. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University1, Melbourne, VIC, Australia; The Florey Institute of Neuroscience and Mental Health, University of Melbourne2, Melbourne, VIC, Australia.

Allosteric modulators represent a novel approach of targeting G protein coupled receptors (GPCRs). Allosteric compounds bind to topographically distinct sites from the highly-conserved endogenous orthosteric pocket, and are capable of modulating both the affinity and efficacy of orthosteric ligands and may have their own intrinsic efficacy1. Despite this, there is little information as to how the allosteric modulators stabilise the high affinity active state of the GPCR-G protein ternary complex. This is in part owing to the limitations of attempting to pharmacologically characterise these interactions in recombinant whole cell assays. These cell-based assays are limited by the inability to control the stoichiometry of the interacting partners (receptor & G protein), and the transient nature of the ternary complex owing to the dynamic nature of the GPCR activation cycle and freely available nucleotides (GDP & GTP) to facilitate these transitions. In order to overcome these issues, we reconstituted the M2 muscarinic acetylcholine receptor (M2 mAChR) into high density lipoproteins (rHDLs), otherwise known as nanodiscs. Nanodiscs provide a reductionist platform, whereby the relative ratio of GPCR and G protein can be controlled thus enabling the system to be pushed to the low-affinity (GPCR alone) or high-affinity (GPCR-G protein ternary complex) state2. Using this approach, we show that allosteric modulators promote the ability of the G protein to stabilise the high affinity active state. Furthermore, whilst allosteric modulators and G proteins both promote the high affinity state in an analogous manner, the allosteric modulator is not able to promote further increases in orthosteric ligand affinity when the receptor is in the high affinity state due to the presence of saturating concentrations of G protein. These results provide increased understanding to how allosteric modulators influence the high affinity state and drive GPCR signalling.


425

Calcium communication in an in vitro model of breast cancer brain metastases

Silke B Chalmers1, Francisco Sadras1, Jodi Saunus2, Sunil Lakhani2, Sarah J Roberts-Thomson1, Gregory R Monteith1 1School of Pharmacy, The Univ. of Queensland, Brisbane, QLD, Australia, 2UQCCR, The Univ. of Queensland, Brisbane, QLD, Australia

Introduction. The brain is unique among sites of breast cancer metastases for poor prognosis, cellular landscape, and limited treatment options. The interaction between breast cancer and brain cells is thought to contribute to metastatic survival and outgrowth, however, the understanding of these interactions is hindered in part by a scarcity of pre-clinical models. Human neural progenitor cells, such as ReNcell VM, can differentiate into matrices of astrocytes and neurons to provide a model of the brain microenvironment suited to high-throughput investigations of cellular pathways. Calcium signalling is deregulated in numerous pathologies, including cancers and their surrounding microenvironment. To date however, the role of calcium signalling in breast cancer brain metastases has been largely unexplored.

Aims. To investigate calcium signalling in breast cancer brain metastases in a high-throughput microenvironment model.

Methods. ReNcell VM stably expressing the calcium sensor jrCaMP1b were differentiated into matrices of neurons and astrocytes. MDA-MB-468 breast cancer cells stably expressing the calcium sensor GCaMP6m were added to neural matrices, and co-cultured for 7 days. Calcium signalling between cell populations was assessed through addition of 10 nM GSK1016790a to stimulate calcium influx selectively in breast cancer cells. Experiments were conducted with an ImageXpress® and single cell data was analysed via MetaXpress and MATLAB.

Results. Addition of GSK1016790a to co-cultures stimulated increased calcium influx in breast cancer cells and ReNcell VM, which was absent in ReNcell VM monoculture. Analysis of single cell signalling events in co-cultured ReNcell VM determined a relationship between increased calcium activity and proximity to breast cancer cells responding to GSK1016790a.

Discussion. This study provides the first evidence of calcium communication between breast cancer and the brain microenvironment, a potential avenue to explore for therapeutic targeting for this disease.

Joyce, J, Quail, D (2017) Cancer Cell 13;31(3):326-341
426
Biased negative allosteric modulators for the calcium-sensing receptor have differential bronchodilator and bronchoprotective effects in mouse precision cut lung slices

Jiayin Diao1, Maggie Lam2, Karen Gregory1,2, Katie Leach1,2, Jane E. Bourke1,2. 1Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash Uni, Parkville; 2Biomed Discovery Institute, Monash Uni., Clayton, VIC, Australia.

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

Aim. To assess CaSR NAM (NPS2143, Pfizer cmpd 1, BMS cmpd 1) bias in CaSR-HEK293 cells and compare NAMs with the β2-adrenoceptor agonist salbutamol for airway relaxation.

Methods. Intracellular calcium (Ca\(^{2+}\)) mobilisation and IP\(_3\) accumulation assays in CaSR-HEK293 cells were used to quantify the affinity and cooperativity of CaSR NAMs. Precision cut lung slices from male C57Bl/6 mice were prepared to visualise changes in airway area after contraction stimulated by 300 nM methacholine (MCh) followed by NAM or salbutamol (bronchodilation assays) or after overnight pre-incubation with 1 μM NAMs (bronchoprotection assays).

Results. CaSR NAMs engendered differential and biased modulation of Ca\(^{2+}\); mobilisation and IP\(_3\) accumulation. CaSR NAMs relaxed pre-contracted airways in a biphasic manner (see figure), with the highest potency first phase of their response being 1000-fold higher potency than salbutamol. Salbutamol and NAMs caused comparable maximal bronchodilation (salbutamol 50±7%, NPS2143 32±8%, Pfizer cmpd 1 70±16%, BMS cmpd 1 48±16%, n=4-6). Overnight incubation with NPS2143 and Pfizer cmpd 1, but not BMS cmpd 1 prevented contraction.

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


427
The effect of single nucleotide polymorphisms on sweet taste receptor expression and cell surface trafficking

Jennifer N. Grant1, Sean S. So1, Nicola J. Smith1 and Angela M. Finch1. School of Medical Science, UNSW1, Sydney, NSW, Australia.

Introduction. The sweet taste receptor (STR) is a family C GPCR consisting of two subunits, T1R2 and T1R3. It is expressed in oral and extra-oral tissues, including the pancreas and gut. The STR subunits are highly polymorphic and four T1R2 single nucleotide polymorphisms (SNPs) occur with ≥ 75% overall allele frequency, including T1R2 I191V and S9C which have been associated with decreased sugar consumption and lower waist-height ratios in obese individuals (Eny et al, 2010; Pioltine et al, 2018). Hence, the STR is a potential novel drug target for treating obesity and type 2 diabetes. However, the underlying mechanism by which these SNPs produce these phenotypes is not known.

Aims. To (i) build homology models of the T1R2 venus flytrap domain (VFD) to predict the effects of the SNPs on ligand binding and (ii) determine the effect of T1R2 I191V and S9C mutations on STR expression and cell surface trafficking.

Method. Using multiple VFD crystal structures as templates, homology models of the hT1R2 VFD were generated and docking of ligands was performed. T1R2 receptors containing either I191V or S9C were transiently transfected into AD293 cells, either alone or alongside wildtype T1R3. Biotinylation pull-down experiments and western blotting were performed to determine the effect of the SNPs on total STR expression and cell surface trafficking.

Results. Assessment of the VFD models indicated that the calcium sensing receptor and the medaka fish T1R3 crystal structures serve as the best templates for generating homology models of the human T1R2 VFD. The homology models predicted that both I191 and S9 are outside of the sucrose binding site. Preliminary results from surface biotinylation experiments suggest that neither T1R2 SNP significantly affected total STR expression or cell surface trafficking though T1R2/T1R3 co-expression appears to result in decreased T1R3 expression.

Discussion. The altered STR expression profile with co-expression of T1R2 and T1R3 may indicate that T1R2 suppresses T1R3 expression in the heterologous expression system used. As the T1R2 SNPs do not appear to alter STR expression or cell surface trafficking, the molecular mechanism underpinning the STR metabolic associations remains elusive.

Expanding the peptide synthesis toolkit to produce bicyclic peptide mimetics for drug discovery
Qingqing Lin1, Denham Hopper1, Haoyue Zhang1, Jordan Syris Qoon1, Zihan Shen1, John A. Karas1, Richard A. Hughes1, Susan E. Northfield1. Department of Pharmacology & Therapeutics, The University of Melbourne1, Melbourne, VIC, Australia

Introduction. The design and synthesis of cyclic peptides is a widely established practice in the field of peptide chemistry. This has been further expanded by the development of orthogonal chemical reactions allowing for production of more chemically complex peptides. We have recently reported a versatile method to produce bicyclic homodimer peptides that are selective mimetics of loops of large proteins, including neurotrophins.

Aims. Use 1,3-dichloroacetone (DCA) to selectively link free cysteine side-chains via an acetone bridge, producing bicyclic dimeric peptides.

Methods. Synthesised six backbone-cyclic peptides, each possessing a single cysteine residue, and created bicyclic dimeric peptides by linking two copies of the cyclic peptide together via an acetone linker using DCA. We systematically investigated a range of reaction conditions, including reaction stoichiometry, peptide concentration, pH and buffer composition.

Results. We were successfully able to identify the optimum conditions for peptide dimerisation for our six peptide sequences and have use these results to produce an overall guide for preparing acetone-linked bicyclic peptides. The peptides were subsequently analysed for proteolytic stability in human serum and were observed to still be fully intact after 48 hours.

Discussion. This study provides valuable insights into the use of DCA as a tool in peptide synthesis. The non-reducible nature of the acetone linker between pairs of cysteine residues makes the DCA dimerisation reaction attractive compared to the better-known disulfide bond approach.

Lin Q et al (2020) ACS Omega 5:1840-1850

Characterisation of the G protein coupling profiles of PAC1 receptor splice isoforms
Jessica J Lu1, Peishen Zhao1, Patrick M Sexton1, Denise Wootten1. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences1, Parkville, VIC, Australia

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

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

Methods. PAC1R isoforms and TRUPATH biosensors were transiently transfected into COS-7 cells and treated with increasing concentrations of agonists: PACAP-38, PACAP-27, vasoactive intestinal peptide (VIP) and maxadilan. Real-time G protein dissociation profiles of Gs, Gi, Gq/11 and G12 were measured at 37°C using PHERAstar (BMG Biotech).

Results. Insertions in ICL3 altered the G-protein coupling profiles of PAC1n and PAC1s. PAC1n-hop displayed a four-fold increase in PACAP-38 potency for Gq/11 coupling (Gq, pEC50: 8.4±0.1; G11, pEC50: 8.3±0.1) compared to PAC1n (Gq, pEC50: 7.8±0.2; G11, pEC50: 7.8±0.2). While, insertions of the hip and hiphop cassettes led to weaker Gi1 coupling. PAC1s increased the potency of VIP-mediated G protein coupling for all four G protein subtypes.

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

430

Understanding GPCR signal compartmentalisation using optogenetic methods

Introduction. Eukaryotic cells possess a limited number of signaling proteins, yet can execute an extensive range of functional outcomes due to the spatiotemporal organisation of intracellular signalling pathways. Spatial compartmentalisation of G protein-coupled receptor (GPCR) signalling results in location-specific production of second messengers that can be recognised by the cell and translated into unique downstream responses. This dynamic concept can be investigated using novel optogenetic methods that offer targeted and highly specific activation of intracellular signalling pathways using light in lieu of ligands.

Aims. Demonstrate that targeting a GPCR to different subcellular locations changes the resultant cellular outcome.

Methods. Subcellular GPCR localisation was validated using confocal microscopy; cellular outcome was quantified using signalling assays and quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Results. The shared structural homology among GPCRs facilitates the modular conjugation of the ligand-sensing and transmembrane domains of one GPCR with the intracellular signaling domains of another. Using this approach, an optogenetic rhodopsin β2-adrenoceptor (opto-β2AR) chimera was created: a light-responsive GPCR that activates the canonical Gs-mediated signalling of the wild-type β2-adrenoceptor. At the plasma membrane, opto-β2AR mimics cyclic AMP (cAMP) production and internalisation comparable to the native β2-adrenoceptor (Siuda et al, 2015). We targeted opto-β2AR to distinct subcellular locations (including early endosomes, golgi and mitochondria) where light activation stimulates cAMP production. Differences in transcriptional responses from spatially distinct pools of cAMP can provide insight as to whether receptor subcellular localisation controls unique cellular outcomes.

Discussion. Disease-relevant GPCR signaling can be location dependant: a greater understanding of signal compartmentalisation will challenge existing conceptions about plasma-membrane delimited signaling and encourage new strategies for GPCR-targeted drug discovery.


431

Differential G protein activation kinetics may underpin the beneficial aspects of clinically trialled A1R atypical agonists
Samantha M McNeill1, Jo-Anne Baltos1, Nevin Lambert3, Paul J White1, Lauren T May3.

Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences1, Melbourne, VIC, Australia; Medical College of Georgia, Department of Pharmacology and Toxicology, Augusta University2, Augusta, GA, USA.

Introduction. Activation of adenosine A1 receptors (A1Rs) represents a powerful strategy for the treatment of cardiovascular disease. Clinically trialled atypical A1R agonists, capadenoson and neladenoson, stimulate cardioprotection (Sabah et al, 2013) with minimal bradycardia (Shah et al, 2019; Sabah et al, 2013), a signalling profile typically attributed to reduced intrinsic efficacy. However, capadenoson and neladenoson are biased A1R agonists (Baltos et al, 2016; Rueda et al, 2020), and as such a better mechanistic understanding is required to facilitate the rational design of more effective A1R therapeutic candidates. Aim. To quantify A1R-mediated Gβγ-effector interactions in response to prototypical and atypical A1R agonists; as Gβγ-GIRK channel interactions are the direct mechanism for A1R-mediated bradycardia. Methods. Stably expressing A1R-HEK293A cells with all G proteins deleted were transiently transfected with masGRKct-nanoluc, GαoA, and Gβγ2-venus. The masGRKct construct readily binds free Gβγ dimers, on a timescale that mirrors GIRK channel activation (Hollins et al, 2009). Results. The prototypical agonist MeCCPA and capadenoson were equipotent with a similar maximal response (pEC50: 6.6 – 6.9; n=3-4, P>0.05). However, the onset kinetics of Gβγ interactions atypical agonists were significantly reduced by 4-8 fold as compared to prototypical agonists (n=3-4, P<0.05). Discussion. Considering the similar potency and maximal response observed for MeCCPA and capadenoson, the different kinetic profile of Gβγ-effector interactions may have a key role in conferring the clinically beneficial profile of atypical A1R agonists.

**432**

**GPCR-CoINPocket2.0: refining the prediction of liganded pharmacological neighbours of unliganded orphan GPCRs**

Sean S So1, Tony Ngo2, Nicola J Smith1, Irina Kufareva1. Orphan Receptor Laboratory, UNSW1; Sydney, NSW, Australia; Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego2, La Jolla, CA, USA.

Introduction. We developed GPCR-CoINPocket (GPCR Contact-Informed Neighbouring Pocket), a crystal structure-informed metric predicting Family A GPCR pharmacological similarity1. In the range of 20-35% sequence similarity (too low for precise homology modelling but adequate for sequence alignment), GPCR-CoINPocket predictions outperform both transmembrane and binding pocket sequence similarity. Nevertheless, some known chemical relationships (e.g. between the CB2 and Y5 receptors) were not captured, indicating that improvements can still be made to the metric.

Aims. Here, we aim to improve the accuracy of GPCR-CoINPocket2 by increasing structure diversity, and developing a new residue comparison matrix (RCM) that more directly reflects residue similarity in ligand-binding characteristics.

Methods. We use large-scale GPCR crystal structure analysis to identify preferred receptor:ligand binding pocket contacts, ChEMBL database analysis to build chemical fragment clusters for RCM construction, and analysis of all structures in the Pocketome4 to reveal preferences in interaction patterns between amino acid fragments and various chemical fragments.

Results. GPCR-CoINPocket now includes 254 structures (up from 116) from 38 GPCRs (up from 27). To reduce data granularity and increase signal, chemical compound fragments were clustered into groups based on their “interchangeability” within different scaffolds where fragment substitution had no or minor effects on the binding affinities to various targets. Backbone, polar, and non-polar distance-based contact strength distributions between fragment clusters and interacting residues were obtained by analysing all liganded structures released up until April, 2018. Work to generate and apply a RCM to GPCR-CoINPocket based on these distributions is ongoing.

Discussion. The development of a residue:ligand contact-based RCM for GPCR-CoINPocket should further improve the predictive accuracy of the metric. Identifying liganded pharmacological neighbours of unliganded orphan GPCRs guides the development of pharmacological tools with which the function and role of orphan GPCRs may be unlocked.


**433**

**Evaluation of meropenem-tobramycin combination regimens against clinical hypermutable Pseudomonas aeruginosa via mechanistic based-modelling and the dynamic hollow fibre infection model**

Akosua A. Agyeman3, Rajbharan Yadav1, Kate E. Rogers1, Vanessa E. Rees1, Yuling Huang1, Anton Y. Peleg2, John D. Boyce1, Antonio Oliver3, Phillip J. Bergen1, Beom Soo Shin4, Roger L. Nation1, Cornelia B. Landersdorfer1

1Pharmacy and Pharmaceutical Sciences and 2Microbiology, Monash University, Melbourne, VIC, Australia; 3Hospital Universitario Son Espases, Palma de Mallorca, Spain; 4School of Pharmacy, Sungkyunkwan University, Korea.

Introduction. Hypermutable Pseudomonas aeruginosa (HYPa) strains occur frequently in patients with cystic fibrosis and are associated with chronic respiratory infections leading to increased morbidity and mortality. These strains have increased mutation rates resulting in multidrug-resistance and treatment failure.

Aims. To characterise bacterial killing and emergence of resistance of clinically relevant meropenem (MER) and tobramycin (TOB) dosage regimens against two clinical hypermutable Pseudomonas aeruginosa isolates at simulated epithelial lining fluid (ELF) concentration-time profiles.

Methods. Hollow-fibre infection model (HFIM) experiments were conducted over 8 days for different dosage regimens of MER and TOB alone and in combinations against CW8 (MIC\textsubscript{MER} = 8 mg/L, MIC\textsubscript{TOB} = 8 mg/L) and CW44 (MIC\textsubscript{MER} = 4 mg/L, MIC\textsubscript{TOB} = 2 mg/L). The total and less susceptible bacterial populations were quantified and subsequently simultaneously described via mechanism-based modelling (MBM).

Results. Monotherapies and low dose combination regimens produced rapid regrowth. The highest daily doses for MER (2 g every 8 h, 3 h infusion) and TOB (10 mg/kg every 24 h, 30 min infusion) in combination demonstrated synergistic killing and resistance suppression below the monotherapy counts over at least 143 h for both isolates. MBM incorporating three bacterial subpopulations and direct bacterial killing by both antibiotics well described the antibacterial effects of the mono- and combination therapies in the HFIM.

Discussion. The MBM which were developed successfully accounted for the time course of amplification of pre-existing less-susceptible bacterial subpopulations. The MER-TOB synergistic combination is promising against clinical HYPa strains and warrants further evaluation.

17
Synergistic ceftazidime and tobramycin combinations for clinical hypermutable Pseudomonas aeruginosa isolates; an innovative dosing approach to enhance bacterial killing and mitigate resistance in a dynamic biofilm model

Hajira Bilal¹, Phillip Bergen¹, Wee L. Lee¹, Anton Peleg², Antonio Oliver³, Roger L. Nation¹, Cornelia B. Landsdorfer¹,². Centre for Med Use and Safety¹, MIPS, Monash Univ.; Dept. Infect. Dis.¹, Central Clinical School, Monash Univ.; Hosp. Univ. Son Espases², Palma de Mallorca, Spain; Drug Deliv Dispos Dynam³, MIPS, Monash Univ., Melbourne, Australia.

Introduction. Pseudomonas aeruginosa chronically infects patients with cystic fibrosis and is associated with increased morbidity and mortality. Ceftazidime and tobramycin are considered first-line treatments. However, hypermutability and biofilm formation results in treatment failure due to selection of resistant mutants.

Aims. We systematically investigated the pharmacodynamic effects of intravenous versus inhalation dosage regimens of tobramycin with and without intravenous ceftazidime.

Methods. Two clinical hypermutable P. aeruginosa isolates CW30 (MIC<sub>CAZ</sub> 0.5 mg/L, MIC<sub>TOB</sub> 2 mg/L) and CW8 (MIC<sub>CAZ</sub> 2 mg/L, MIC<sub>TOB</sub> 8 mg/L) were investigated for 120 h in the dynamic in vitro CDC biofilm reactor. Clinically relevant treatments were: continuous infusion ceftazidime 9 g/day (33% lung penetration); intravenous tobramycin 10 mg/kg Q24h (50% lung penetration); and tobramycin 300 mg Q12h as inhalation, and their combinations. Total and less-susceptible planktonic and biofilm bacterial counts were carried out over 120 h. Ceftazidime and Tobramycin were quantified by LC-MS/MS.

Results. All treatments in monotherapy were ineffective for both isolates, with a regrowth of planktonic (≥4.7log<sub>10</sub> CFU/mL) and biofilm (≥6.6log<sub>10</sub> CFU/cm²) bacteria, and amplification of less-susceptible planktonic and biofilm bacteria by 120 h. Both combination treatments demonstrated synergistic bacterial killing, not only for planktonic but also biofilm bacteria; however, greatest bacterial killing against both modes of bacterial growth was observed with the combination simulating tobramycin inhalation. In addition, the combination regimen resulted in a very substantial suppression of resistance of planktonic and biofilm bacteria to each of the antibiotics for both isolates.

Discussion. Thus, ceftazidime combinations with intravenous or, especially, inhaled tobramycin hold promise to treat biofilm bacteria to each of the antibiotics for both isolates.

Effect of high Drug Burden Index polypharmacy on physical function and daily activities: male and female, young and old mice.

John Mach¹,²,³, Harry Wu¹,²,³, Gizem Gemikonakli¹,²,³, Trang Tran¹,³, David G Le Couteur³,⁴ & Sarah N Hilmer¹,²,³. Laboratory of Ageing and Pharmacology, Kolling Institute, Sydney, NSW, Australia. ¹. Clinical Pharmacology and Ageing, Royal North Shore Hosp, Sydney, NSW, Australia. ². Northern Clinical School, Univ of Sydney, Sydney, NSW, Australia. ³. ANZAC Research Institute Sydney, NSW, Australia. ⁴.

Introduction. Polypharmacy (use of ≥ 5 drugs) and increasing DBI (DBI: measure of total exposure to anticholinergic and sedative drugs) are associated with impaired physical function, dependence in daily activities and increased frailty in observational studies of older adults. The effect of polypharmacy on sex is unclear.

Aims. To determine the effect of high DBI polypharmacy on these outcomes in male and female, young and old mice.

Methods. Young (Y, 2.5 months) and old (O, 21.5 months) male (M) and female (F) C57BL/6 mice received control (C) feed or following polypharmacy (p<0.05). Compared to control, polypharmacy significantly reduced nesting ability in old female and male mice and biofilm bacteria to each of the antibiotics for both isolates.

Discussion. Thus, ceftazidime combinations with intravenous or, especially, inhaled tobramycin hold promise to treat challenging infections caused by hypermutable P. aeruginosa strains and warrant clinical investigation.
The role of UGT enzymes as novel modulators of lipid biosynthesis and SREBP signalling in breast cancer


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

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

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

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

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

Survey of how and why students use resources in a pharmacology course

Sheila A Doggrell. Faculty of Health, Queensland University of Technology, QLD4178

Introduction. Students can often select between a variety of resources e.g. attending face-to-face lectures, accessing lecture recordings, and standalone Powerpoints.

Aims. To survey students to determine how and why students use these resources in a pharmacology course.

Methods. Online survey, with students studying pharmacology to tick all that apply.

Results. The study was undertaken in 2017 and 2019. Only 17% of students consented to undertake the study. About half of the students attended lectures. The three most common reasons for attending lectures were ‘It allows for interaction with unit staff and/or students’, ‘I am concerned that recordings may not be complete or the technology for recording may fail’ and ‘I think I learn more by attending’. For those students who accessed lecture recordings as well as attending lectures, the two most common responses were ‘Revise lecture concepts for assessment purposes’ and ‘clarify difficult concepts’. For those students who did not attend lectures, reasons for not attending; ‘I don’t like the lecture theatre environment’ and ‘I don’t like the lecture time – it was too early/late’. Those that did not attend lectures but accessed lecture recordings; ‘I prefer the flexibility of the online recordings’ and ‘I don’t like the lecture theatre environment’. The final question on the survey was to ask the students to add any additional comments or feedback they had on the use of lecture recordings as a learning tool, and the main themes were ‘flexibility’ and ‘useful’. A high percentage of students used standalone Powerpoints as a resource, mainly to study prior to assessment or exams.

Discussion. Despite consent being sought in workshops and lectures, which were both poorly attended, and online, the number of participating students was low. However, as the consenting students had similar marks to the overall class marks, the participants may have been representative of the class. In conclusion, it seems appropriate to supply students with a range of resources, as individual students use them and appreciate them for a range of reasons.
438

An examination of extemporaneous compounding skills, knowledge and confidence progression from undergraduate to practice: a pharmacy education perspective
Quang Hung Duong, Gabrielle Jin Rou Pang, Rachel Roy, Charles Wei-Dong Xin, Suzanne Caliph. Dept of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, VIC

Introduction: Extemporaneous compounding is a required component of the pharmacist registration. A competent pharmacist is expected to have appropriate education, training and skills to undertake extemporaneous compounding of safe and efficacious products. While there have been some studies on compounding practice of pharmacists, little is known about the educational aspect of extemporaneous compounding such as how pharmacy students perceive their training and progression from undergraduate to internship.

Aim: Our study aimed to examine how pharmacy students, interns (pre-registrant pharmacy graduate) and pharmacists perceived their competency in extemporaneous compounding of pharmaceutical products.

Methods: We designed and conducted a self-administered survey with undergraduate pharmacy students, interns and pharmacists. Using a Likert-scale, participants ranked how confident they felt in compounding a selection of extemporaneous products. The data were then analysed with Kruskal-Wallis test. Participants’ opinions on areas of improvement of extemporaneous compounding teaching were also recorded as free-text responses.

Results: 27 undergraduate students, 7 interns and 7 pharmacists completed the questionnaire. Compared to students, pharmacists perceived themselves to be significantly more confident in compounding suppositories and pessaries (p = 0.013), while showing no statistical differences in other products such as solutions, suspensions, creams and ointments. There was no significant difference between perceptions of undergraduate students and interns on their competence to compound “simple” pharmacy products. Various factors contributed to participants’ perceptions including level of knowledge, training and experience. Suggestions to improve teaching extemporaneous compounding curriculum included frequent laboratory-based practice, integration of theoretical knowledge, legislation, fostering soft skills and clinical aspects.

Discussion: Pharmacy students participated in our study perceived they could competently perform simple compounding of pharmaceuticals. Nonetheless, extemporaneous compounding curriculum can further be improved enhanced to optimize student knowledge, skills and learning experiences in this unique area of professional practice.

439

Communicating health risks of nicotine vaping products: a systematic review of message content, format, and source on harm perception and behavioural intentions
Daniel A Erku1, Linda Bauld2, Lynne Dawkins3, Coral E Gartner4, Kathryn J Steadman1, Seth M Noar5, Shakti Shrestha1 and Kylie Morphett4 1School of Pharmacy, University of Queensland, Brisbane, QLD, Australia; 2Usher Institute and SPECTRUM Consortium, College of Medicine and Veterinary Medicine, University of Edinburgh, Scotland; 3Centre for Addictive Behaviours Research, School of Applied Sciences, London South Bank University, London; 4School of Public Health, University of Queensland, Brisbane, QLD, Australia; 5Hussman School of Journalism and Media, University of North Carolina at Chapel Hill, Chapel Hill, NC

Introduction. Effective ways of communicating relative risks of various nicotine-containing products can help increase the accuracy of relative harm perceptions of nicotine vaping products (NVPs) compared with combustible cigarettes and increase smokers’ intentions to quit smoking and/or to switch to vaping.

Aims. To systematically review the literature on (1) whether and how various risk messages about NVPs alter harm perception and behavioural intentions of smokers and non-smokers, and (2) how trust in sources of NVP risk communication affects message reception and behavioural intentions.

Methods. Seven electronic databases (PubMed, PsycINFO, EMBASE, Web of Science, Communication & Mass Media Complete, CINAHL, and Google scholar) and reference lists of relevant articles were searched for articles published up to April 2020. Experimental, quasi-experimental, and cross-sectional studies were included. The Newcastle–Ottawa Scale and the Evidence Project Risk of Bias Tool were employed to assess the quality of observational and intervention studies, respectively. Key findings were extracted and grouped into subcategories according to the Message Impact Framework.

Results. Nicotine addiction messages resulted in greater health and addiction risk perceptions, relative risk messages comparing the health risks of NVPs to cigarette smoking increased the perception that NVPs are less harmful than combustible cigarettes, and a nicotine fact sheet corrected misperceptions of nicotine and NVPs. Experimental studies found that smokers’ intention to purchase, try or switch to NVPs was higher when exposed to a relative risk message and lower when exposed to nicotine addiction warnings. Trust in NVP risk information from public health agencies was associated with lower odds of: i) NVP use, and ii) perceiving NVPs as less harmful, whereas those who trusted information from NVP companies were more likely to perceive NVPs as less harmful than combustible cigarettes.

Discussion. Our findings suggest that relative risk messages can help improve the accuracy of harm perceptions of NVPs and increase smokers’ intentions to quit smoking and/or to switch to vaping, although the literature is nascent. Future research should explore the most effective way of pairing relative risk messages with warning labels (such as nicotine addiction) in order to maximize potential public health benefits while minimizing unintended consequences.
Integrating virtual simulation (MyDispense) for teaching comprehensive care pharmacy curriculum.
Betty Exintaris, Rita Wardan, Annie Chen, Sara Chuang, Nilushi Karunarathne, Vivienne Mak. Monash Institute of Pharmaceutical Sciences, Melbourne, VIC, Australia

Introduction. The integration and application of knowledge to solve medication-related problems is a critical skill for pharmacists. This skill is commonly taught through case-based teaching. However, this technique does not require students to gather and summarise all relevant patient-specific information on their own. MyDispense, a web-based pharmacy simulation program, allows students to assume the role of a pharmacist to evaluate, verify, and dispense a prescription in a virtual pharmacy setting.

Aims. To utilise new and existing case-based teaching material to create MyDispense simulation activities to teach 2nd year comprehensive care (CC) Pharmacy curriculum.

Methods. In the latter half of 2nd year, Pharmacy students undertake a unit focused on knowledge and skills required for the diagnosis and therapeutic management of patients with various endocrine and renal conditions. New and existing case materials were adapted to create two standard MyDispense teaching activities that were integrated into the endocrine and renal CC curriculum. A third MyDispense activity was created and integrated into a cardiovascular focused CC unit which focussed on the integration of knowledge across CC units (thyroid, diabetes and hypertension).

Results. During the adaptation phase, two Clinical Practitioners reviewed existing case-based teaching material and incorporated new elements to the cases, focusing on appropriateness of therapy based virtual history taking, thereby simulating the identification, resolution and documentation of medication related problems. A secondary review was conducted and cases were built onto the MyDispense web-based platform by an experienced pharmacist. Cases were designed with a primary focus of teaching contraception and diabetes patient-centred management and counselling. The complex case produced allows students to apply their knowledge of management of a complex range of ailments. In addition, the design of the complex case included real-life complexities such as prioritisation of tasks, conflict resolution and necessity of patient centred care to better simulate an authentic experience.

Discussion. Virtual simulations such as MyDispense, offer an authentic teaching tool for Pharmacy curriculum. The standardised experience will allow the authors to evaluate students’ perceptions on the effectiveness of using a virtual simulation (Mydispense) to improve patient-centred care.

Implementing and Evaluating a Course in Professional Ethics for the Undergraduate Pharmacy Curriculum in Jordan
Leen B. Fino1,2, Ahmad Alsayed2, Iman A. Basheti1,2, Bandana Saini3, Rebekah Moles3, Betty B. Chaar1. The University of Sydney1, School of Pharmacy, Faculty of Health and Medicine, Sydney, NSW, Australia; Applied Science University2, Faculty of Pharmacy, Amman, Jordan

Introduction. Today, pharmacy practice mandates “patient centred care” at a fundamental level. This patient centeredness assigns a higher level of responsibility for pharmacists. It is expected pharmacists are able to handle challenges competently and in the best interests of the patient. These challenges often involve ethical principles, institutional, personal or other constraints that can pull practitioners in incompatible opposite directions, leading “ethical dilemmas” in many circumstances. Literature underlines the positive impact of educational interventions focussing on ethical awareness and competence, and that ‘gaps’ were found to exist in pharmacy training/curricula for Jordanian pharmacists.

Aims. To develop, implement and evaluate the utility of a carefully designed ethics education component in pharmacy undergraduate curriculum for a cohort of pharmacy students within a well-ranked Jordanian University.

Methods. Fifth- year pharmacy students at ASU Applied Science Private University in Jordan, attending Summer Pharmacy School from July- September 2020 were invited to participate in an educational intervention (the delivery of a suite of didactic lectures online, followed by skills-based workshops online, to enable translation of theory into practice). This study was delivered in three main phases, with a pre-test and post-test survey administered immediately before and after the educational intervention. And focus-group discussions at the end to elicit students’ feedback.

Results. Preliminary data indicated enhanced levels of confidence in students’ decision-making. Moreover, the development of students’ moral reasoning and decision-making skills were also observed to be enhanced.

Discussion. This study highlighted the importance of the implementation of an ethics course in pharmacy undergraduate curricula. This course made a positive impact on the students learning experience and provided a strong environment for discussion and group learning.
**442**

**Development and delivery of a pharmacology fundamental unit for first-year undergraduate students**

Marina Santiago. Department of Biomedical Sciences, Macquarie University, Sydney, NSW, Australia

Introduction. In 2016, the Faculty of Medicine and Health Sciences released the Bachelor of Clinical Science, an innovative and accelerated degree with the aim to build foundational skills needed for a career in health. Pharmacology was not initially taught in this degree but during the first review in late 2017, I have strongly recommended the addition of a fundamental pharmacology unit due to clear benefit it would bring to future health professionals. The review process led to a curriculum redesign which included a pharmacology fundamentals unit to be implemented in 2019. The challenge became to teach pharmacology in an engaging manner to a cohort of first-year students without a good understanding of molecular biology and physiology. This was further aggravated by COVID-19 in 2020, which required changes to deliver the unit fully online as well as mixed mode.

Aims. To describe the process and considerations during development and delivery of a pharmacology fundamental unit to first-year Bachelor of Clinical Science students.

Methods. I have combined my teaching philosophy “Too much information is no information thus it is about quality, not quantity; and focus on keeping it relevant”, and the information provided in the literature and by colleagues to develop this unit. I kept the material to the minimum focusing on important pharmacological concepts and integrated several games and clinical scenarios to engage the students. I also developed and implemented a pharmacodynamics online module for revision (student-centred approach). Short summative quizzes were developed to provide continuous feedback to the teaching staff on what is not understood specially considering the lack of basic knowledge in other related subjects. To keep it relevant to their future desired careers, one of the assessments is a group role-play where students must interpret drug profiles and apply knowledge acquired. Last, with the changes under COVID-19 restrictions, activities were modified to be available fully online (via zoom and teaching platform) to guarantee equity as some students are enrolled fully online because of health concerns around attending face-to-face tutorials.

Results and Discussion. Formal and informal feedback from students show that the unit has been well received. Students praised game-based approach and activities where clinical scenarios were used. In the current delivery, students appreciate the effort to deliver similar material to both face-to-face and fully online cohort. Formal feedback obtained this year will be used to better evaluate the online delivery and further improve this unit in 2021.

**443**

**Practising teamwork begins in the classroom: tools to evaluate teamwork behaviour in small group activities**

Nilushi S Karunaratne1. Faculty of Pharmacy and Pharmaceutical Science, Monash University1, Melbourne, VIC, Australia.

Introduction. Teamwork is a highly sought ‘soft-skill' of graduates entering the workforce. In the classroom, students may work in groups but often forgo the opportunity to practise and develop teamwork behaviours to enable shared goals and shared learning.

Aim. To use a targeted approach to support the development of teamwork skills in undergraduate students using Comprehensive Assessment of Team-Member Effectiveness (CATME) and FeedbackFruits teamwork evaluation tools.

Methods. Numerous units at the Faculty of Pharmacy and Pharmaceutical Science at Monash University involve students working in semester-long predefined teams during small group teaching activities. Initially, students were taught effective teamwork, establishing team expectations and setting ground rules in the form of a team contract. Web-based team member evaluation tools CATME and FeedbackFruits were then embedded into units featuring small group work to provide information, demonstration, practice and feedback to students on various teamwork behaviour attributes.

Results. Since 2017, when the Faculty opted for a uniform approach to the evaluation of team member performance in team tasks, CATME has been utilised in 23 individual units across the two undergraduate degrees offered at the faculty. Subsequently, CATME was embedded within units to allow students the opportunity to evaluate, moderate and remediate their teamwork behaviour where needed. Positive reinforcement from students on the value of CATME for individuals working in teams and ability for instructors to monitor team dynamics and moderate individual grades for team tasks has seen the use of CATME grow over the last four years (see Figure 1). This year FeedbackFruits was piloted in 5 units across the faculty as an alternative tool for teamwork evaluation.

Discussion. Both CATME and FeedbackFruits offer useful tools to support teamwork behaviour development in students. FeedbackFruits provides a suite of additional tools such as peer review, interactive document and interactive presentation, making this web-based platform attractive for use in undergraduate curriculum.
Prevalence and predictors of health information overload in patients with a chronic condition: A national survey

Israa Khaleel1, Kenneth Lee1,2, Gregory M. Peterson1, Syed Tabish Razi Zaidi1,3, Barbara C. Wimmer1. School of Pharmacy and Pharmacology1, University of Tasmania, Tasmania, Australia; Division of Pharmacy, School of Allied Health, Faculty of Health and Medical Sciences2, University of Western Australia, Western Australia, Australia; School of Healthcare, Faculty of Medicine and Health3, University of Leeds, West Yorkshire, England.

Introduction. With the rapid growth of health information, patients with a chronic condition (e.g. diabetes) are at risk of developing health information overload (HIO). Generally, HIO can be defined as the point where the volume of the information exceeds the information processing ability of a particular individual. Feeling overloaded can impact processing and decision-making when dealing with health information.

Aims. This study aims to quantitatively determine the extent of HIO in Australian patients with diabetes, and to identify predictors of HIO in these patients.

Methods. Participants were recruited to take part in an online Australia-wide survey through Facebook from Dec 17th 2019 to Jan 2nd 2020. Inclusion criteria: adults aged 18 years and above, living in Australia, diagnosed with diabetes, and searching for, receiving or utilising health information regarding their diabetes in the English language. The Cancer Information Overload Scale was adopted (5 items using 5 point-Likert scales; total score from 5 to 25) to measure levels of HIO. A multiple linear regression model was used to identify the study variables that were associated with HIO.

Results. Of 455 participants, 73.2% were female and 60.8% were married or in a domestic partnership. The mean age of participants was 59.2±11.1 years. Preliminary data analysis showed that participants had a mean score of 14.2±4.33 for HIO. The following variables were significantly associated with HIO: type of DM (0.157, CI: 0.526-2.771), treatment burden (0.308, CI: 0.111-0.218), health literacy (-0.190, CI: -2.723- -0.783), and e-health literacy (-0.129, CI: -0.133- -0.012). Discussion. Our findings will help in providing deep insights into the prevalence, predictors and effects of HIO in patients with diabetes. The research outcomes will help healthcare professionals in terms of providing suitable amount of information that can be effectively used by patients with chronic health conditions.

Students in the driving seat – online delivery of real time interactive practical classes

Makhala Khammy, Michael J Lew, Mark Habgood. Dept of Pharmacol, Univ of Melbourne, Parkville, VIC, Australia.

Introduction. The undergraduate level 3 subject, Drugs in Biomedical Experiments, is a practical-based subject that exposes students to the experimental basis of scientific enquiry and enables them to develop skills relevant to contemporary biomedical research. The COVID-19 pandemic and health measures to limit community transmission have presented considerable challenges for delivering practical class teaching when students are unable to be physically present in the laboratory to conduct experiments.

Aim. Our aim was to redesign for online delivery, practical classes that challenge and engage students in enquiry-based learning and fulfill subject learning objectives.

Methods. Pre COVID-19, students worked collaboratively in groups to formulate hypotheses that could be investigated using isolated tissues in tissue organ bath systems. We adopted a novel approach of using proxies in the practical class to physically conduct experiments under the direction of groups of students who attend live via the video conferencing platform, Zoom. Chart recordings of tissue responses were live-streamed to students enabling them to instantaneously observe and interpret generated data. Data files were provided to students for data analysis via the Learning Management System.

Discussion. Use of proxies enabled student-designed experiments to be conducted in real-time during practical sessions. Anecdotal evidence suggests that student engagement is enhanced by the ‘real’ nature of the experiments and the ability to visualise in real-time, pharmacological phenomena of their own design. Live streaming of the chart recorder and upload of data files provided the flexibility for student groups to adjust or extend their experimental protocols accordingly. Key enabling factors were (a) maintaining the same online groups throughout the course to enable students to build rapport and develop interpersonal collaborative learning skills (key graduate attributes), and (b) providing several lead in online workshops, video and CAL based lessons to equip students with sufficient background knowledge of quantitative pharmacological analysis and relevant tissue systems to develop their own hypotheses and experimental plan. Online practicals are prone to student disengagement. Here, we adopted an innovative approach to deliver real time interactive practical classes online that were successful in engaging students and fulfilling the desired learning outcomes.
Using PollEverywhere and content chunking during remote delivery in an undergraduate course

Iris Lim1, Faculty of Health Sciences & Medicine, Bond University1, Gold Coast, QLD, Australia

Introduction. In line with the COVID-19 lockdown and social distancing policies, most educational institutions have suspended face-to-face learning activities. Academics are challenged to embrace digital pedagogy while creating and improving effective student engagement strategies to ensure learning enhancement in an online space.

Aims. The aim was to optimise the usage of the PollEverywhere online app as a tool to improve content chunking in remote lecture sessions.

Methods. Lecture notes were uploaded to the Learning Management System (Blackboard Ultra) prior to the lectures for optional reading. Topic introductory videos (5–7 minutes) were also made available for mandatory viewing. The weekly 2-hour lecture sessions were delivered synchronously via Blackboard Collaborate. The content was carefully divided into 20–25 minute sections, followed by 3 to 4 Multiple Choice and True/False Questions displayed using the PollEverywhere plug-in within Microsoft PowerPoint (see figure). A timer of one minute was set for each question to allow students to enter their answer using the PollEverywhere app on their smartphone or via the website link. Correct answers were then displayed and further discussed by the educator. Students were encouraged to register under the PollEverywhere system for identification, as their number of correct answers were tallied at the end of every session.

Results. Both quantitative and qualitative feedback from students indicated that this teaching approach was highly valued. Retention of ‘live’ participants in the remotely delivered lecture sessions were maintained throughout the semester, similar to that of face-to-face lectures in previous semesters. To encourage participation in this activity, a ‘Top 10 PollEverywhere Leaderboard’ was updated weekly in the course site and at the end of the semester, the three students with the highest scores received prizes in the form of online gift cards.

Discussion. Using polling and content chunking appears to be an effective way to maintain student engagement in a digital space and retaining student attendance and participation in synchronous teaching sessions.

iiBalls: an updated and expanded iris simulation to teach autonomic pharmacology and diagnostic ocular drugs

Graham A. Mackay1, Terry Judd2, Peter Crack1, Michael Lew1, James Ziogas1, Bang Bui3. Pharmacology and Therapeutics1, Medical Education2, Optometry and Vision Science3, University of Melbourne, Parkville, VIC, Australia.

Introduction. The smooth muscle of the iris, with resultant change in pupil diameter, provides a clear means of illustrating the activity of the autonomic nervous system and its associated pharmacology. In addition, differential reactivity to a range of pharmacological agents is an important part of the diagnosis of many ocular conditions. We have previously generated an iris simulator (iBalls) and have successfully used this in teaching both Science and Optometry students. This simulator was further refined and then marketed by Sheffield Bioscience Programs. Here, we have updated and expanded iiBalls to incorporate drug choices that are better aligned with optometry practice and expand the clinical cases to reflect the broad utility of drugs in an ocular diagnostic setting.

Aim. To generate and evaluate an engaging and clinically accurate computer simulation of the iris to better teach autonomic pharmacology and ocular diagnostics.

Methods. The iris simulator, choice of clinical cases and drug selection were developed and implemented by an interdisciplinary team. Given the strong relevance to optometry practice, the simulator was initially evaluated by year 2, Doctor of Optometry students, as a component of subject “Pharmacology for Health Professionals”. Given its introduction in Semester 1, 2020, the class was run as a synchronous Zoom session. A brief anonymous questionnaire was used as the evaluation instrument. In this first iteration, no comparisons with the prior or alternative simulators were conducted.

Results. Student feedback was positive, confirming that the cases (e.g. Horner’s syndrome, myasthenia gravis, Adie’s tonic pupil) were highly engaging and relevant, and enabled them to better understand and apply the autonomic pharmacology lecture content they had received.

Discussion. An updated iris computer simulation (iiBalls) was generated and trialled with initial positive feedback. Future work aims to more comprehensively establish the learning efficacy of this new simulator not only for optometry students, but also for other student cohorts where understanding autonomic pharmacology is important.
Exploring Transitional Challenges in Preparing Pharmacy Students for Practice

Anna Dionisiou1, Daniel Grimes1, Aisling McEvoy1, Wendy Yao1, Brodie Yelds1, Adam Phillips2, Ian Bates2, Mike Munday2. Faculty of Pharmacy and Pharmaceutical Sciences, Monash University1, Parkville, VIC, Australia; School of Pharmacy, University College London2, Bloomsbury, LDN, United Kingdom.

Introduction: Pharmacy, at its core, is an amalgamation of many specialties, the subjects of which are often separate degrees. From an education perspective, pharmacy is uniquely problematic to define; it is difficult to draw a line between what is necessary to create ‘medicines experts’, and what is superfluous in preparing students for practice.

Aim: We aim to discover the core challenges faced by pharmacy students and pharmacists in their transitions to university and clinical practice, allowing future enhancements within pharmacy education to better prepare pharmacy students for practice.

Method: Our study employed a qualitative descriptive study design using interviews to gather information from student, pre-registration, and registered pharmacists concerning their education and practice experiences.

Results: The participants attributed the main challenges of their transition to university (n=46) and registered practice (n=18) involved being in a new environment, familiarity and application of knowledge, availability of support, and time management. Many participants identified having additional placements would supplement their pharmacy education and strengthen both clinical and non-clinical skills.

Discussion: It appears that students need more preparation and assistance to ensure smoother and more successful transitions in their careers. It is important for pharmacy degrees to change to reflect pharmacists’ evolving scope of practice. Enhancing the development of high quality pharmacy graduates will result in pharmacist’s who are prepared to embrace the diversity of pharmacy practice.

Improving communication with patients with regards to the risk of SGLT2 inhibitor-associated diabetic ketoacidosis

Tamara Y Milder1,2,3,4, Sophie L Stocker2,4, Melissa Baysari5, Richard O Day2,4, Jerry R Greenfield1,3,4. Department of Diabetes and Endocrinology, St Vincent’s Hospital1, Sydney, NSW, Australia; Department of Clinical Pharmacology and Toxicology, St Vincent’s Hospital2, Sydney, NSW, Australia; Diabetes and Metabolism, Garvan Institute of Medical Research3, Sydney, NSW, Australia; St Vincent’s Clinical School, University of NSW4, Sydney, NSW, Australia; Faculty of Medicine and Health, The University of Sydney5, Sydney, NSW, Australia.

Introduction. It is important that patients are informed and aware of situations to withhold their sodium-glucose cotransporter 2 (SGLT2) inhibitor (acute illness and pre-surgery) to reduce the risk of diabetic ketoacidosis (DKA).

Aims. To explore the safety advice that general practitioners (GPs) and endocrinologists provide to patients taking SGLT2 inhibitors, and to explore patients’ understanding of these safety issues.

Methods. Semi-structured interviews were conducted with 14 GPs, 11 endocrinologists and 13 patients taking SGLT2 inhibitors for type 2 diabetes. A snowballing approach was used to recruit GPs and endocrinologists. Emergent themes were identified from the transcripts.

Results. There are potential barriers to patients being aware of situations to withhold their SGLT2 inhibitor, particularly the situation of acute illness with reduced intake. These barriers include variable awareness and knowledge of the risk of DKA at a primary healthcare level. Additionally, if patients are informed of the risk of DKA and situations to withhold their agent, this information is often only provided at the time of prescription and in verbal form. Patients are generally not questioned in subsequent consultations about their understanding of the information initially provided. Therefore, potential knowledge deficits are not addressed. Furthermore, Consumer Medicine Information leaflets are generally not perceived by patients to be an effective means of communicating safety issues because of the volume, technicality and font size of the material.

Discussion. To improve patients’ awareness of ways to reduce the risk of SGLT2 inhibitor-associated DKA, their needs to be ongoing education of GPs by endocrinologists about this serious adverse effect including risk factors for its occurrence. We recommend that following the prescription of an SGLT2 inhibitor clinicians question their patients about their understanding of situations to withhold their agent as this may identify that further reinforcement regarding this issue is required.
450
COVID-19 and emergency online delivery: What worked for a pharmacology course?
Suong NT Ngo1. School of Animal & Veterinary Sciences, The University of Adelaide1, Adelaide, SA, Australia.

Introduction. The COVID-19 represents unique challenges to the education sector across the globe. Due to restrictions advised by the Australian health and foreign affairs authorities, including suspension of all in person class-room activities, Australian universities have transitioned to remote teaching and learning in Semester 1 2020.

Aims. The aim of this study is to describe the emergency move to online delivery of a pharmacology course and highlight the teaching approaches implemented during the COVID-19 pandemic to maintain education of students.

Methods. Within the basic structure of social distancing, compulsory online lecture delivery, and cancelling or postponing of all in class-room tutorials and practical classes, as course co-ordinators, we defined the scope of delivery issue and feasibility and proposed effective solutions for continuing delivery of lectures, tutorials, and practicals remotely.

Results and Discussion. A total of 58 DVM (Doctor of Veterinary Medicine) students were enrolled in the Pharmacology course in 2020. Before restrictions, the course was taught via three main in-person activities until week 4 of Semester 1, which include lectures, tutorials and practical classes comprised of clinical case studies and drug calculations. From week 5, the 23rd March 2020, the course was moved to on-line completely. Lecture recordings, produced by Echo360 universal, were posted online for students before the scheduled lectures time, at each of the teaching weeks via MyUni. Timed-online quizzes (1 hour duration/each, in MCQs & SAQs format) were administered via MyUni to replace face to face tutorials, supplemented with “summaries of key points” from lectures and “tutorial practice questions”, both in pdf files made available online for students to access via MyUni. Online practicals (3 hour duration/each) were administered via MyUni using discussion boards, with the use of google docs to facilitate group discussion and report writing. Additional zoom meetings with students were also provided to clarify lecture, tutorial contents if needed, also allowing students to ask questions. All online class activities were maintained as per the regular weekly timetable as scheduled at the beginning of the semester, with no change to timing of lectures, tutorials or practicals.

Conclusion: In summary, the pharmacology course was successfully delivered in Semester 1, with all teaching activities completed timely. All 58 DVM students sit the primary online final exam and successfully completed the course.

451
Type 2 diabetes – A risk of underdiagnosis in those with risk factors for diabetes
Emily G Pickering1,2, Elizabeth Steels1,2, Kathryn J Steadman1. School of Pharmacy, The University of Queensland1, Brisbane, QLD, Australia; Evidence Sciences Pty Ltd2, Brisbane, QLD, Australia.

Introduction: Glucose dysregulation refers to a group of conditions on a continuum that starts with early impaired fasting glucose (IFG) with further dysregulation preceding diagnosis of Type 2 diabetes (T2D)[1]. A person may be asymptomatic for many years before diagnosis and have some of the complications, including cardiovascular disease, retinopathy and neuropathic pain before diagnosis. For the general practitioner, the lack of recognisable risk factors, and the potential for standard diagnostic tools to provide an incorrect diagnosis, may lead to a small number of people being incorrectly diagnosed and fail to have appropriate measures in place to prevent complications[1, 2].

Methods: To assess reliability of fasting blood glucose (FBG) (assessing liver function in the fasting state) and post-prandial blood glucose (PBG) (assessing the fed state glucose metabolism dynamics) in people with a risk factor of T2D.

Results: The preliminary results from 242 separate glucose tolerance tests has indicated 10% discrepancy between the results of the FBG tests and the PBG tests.

Discussion: These results indicate that FBG levels, when used a single diagnostic marker without taking into account other risk factors, may be underestimating the prevalence of pre-diabetes or T2D by up to 10% in Australians and that further investigations should be performed for those with risk factors for T2D.

Meat in the sandwich? – Effect of the pharmacy residency program on pharmacy educators
Chih Yuan Wang1, Alexandra Clavarino2, Sonya Stacey3, Karen Luetsch1. School of Pharmacy1, School of Public Health2, The University of Queensland, Brisbane, QLD, Australia; Children’s Health Queensland Hospital and Health Service3, Brisbane, QLD, Australia.

Introduction. A residency training program for early career hospital pharmacists was introduced by the Society of Hospital Pharmacists of Australia (SHPA) in Australia in late 2016, modelled on similar programs in other countries. Hospital pharmacy educators have the role of implementing the program’s vision, reconciling workplace and pharmacy resident needs and demands.

Aims. This qualitative study explored pharmacy educators’ early experiences in implementing the SHPA pharmacy residency program and their navigation of potentially conflicting needs of workplaces and residents.

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

Results. Fourteen pharmacy educators and clinical pharmacists involved in implementing and delivering the pharmacy residency program participated in this study. Educators involved in the SHPA residency program identified that it provides a framework to structure the workplace based development of early career pharmacists. The implementation of the program placed significant demand on resources in workplaces which led to unexpected trade-offs, with residents having priority access to certain training opportunities. This led to concerns about the inadvertent development of a two-tiered system, in which educators have to reconcile limited resources and equitable access to developmental opportunities for resident and non-resident pharmacists.

Discussion. The SHPA pharmacy residency provides a structure for workplaces to implement consistent workplace based training for early career hospital pharmacists. Due to extra demand on resources and hospital pharmacy educators, who are generally the implementers of the program, potential risks of preferencing pharmacy resident training and opportunities over others need to be monitored and mitigated for.

The FFA4 agonist TUG891 relaxes mouse airways by inhibiting calcium oscillations but not sensitivity in precision cut lung slices.
Liam P Allan, Maggie Lam, Chantal Donovan, Ralph A Angeles, Simon G Royce, Jane E Bourke. Dept of Pharmacology, Monash University, Melbourne, VIC, Australia.

Introduction. Excessive contraction of airway smooth muscle is a key feature of asthma pathophysiology, mediated by the parallel signaling pathways of calcium oscillations (due to release and reuptake by the sarcoplasmic reticulum) and calcium sensitivity. The β2-adrenoceptor agonist salbutamol (SALB) inhibits both pathways, resulting in bronchodilation. However, its efficacy is reduced with increasing disease severity, prompting the need to identify novel dilators. The G-protein coupled receptor free fatty acid 4 (FFA4), expressed in airway smooth muscle, is activated by the synthetic agonist TUG891. The aim of this study was to compare bronchodilator responses to TUG891 and SALB and define the effects on of TUG891 on methacholine (MCh)-induced calcium oscillations and sensitivity.

Methods. Male 6-8 week BALB/c mice were euthanised, their lungs inflated with agarose and sliced with a vibratome to make precision cut lung slices (PCLS, 200-250µm thickness). Airway responses were measured as changes in airway area using phase contrast microscopy. Concentration-response curves to TUG891 and salbutamol were prepared in perfused PCLS after airways pre-contracted with MCh. To assess the effects of TUG891 on calcium sensitivity alone, some PCLS were treated with caffeine/ryanodine (caff/ry) to abolish MCh-induced calcium oscillations. Separate PCLS were loaded with SBP and Oregon green dye and fluorescence imaging was used to capture the effects of TUG891 on the increase in frequency of calcium oscillations induced by MCh.

Results. TUG891 was ~25% more efficacious than salbutamol in mice PCLS, with a lower potency (5.8±0.2, n=5) than salbutamol (4.9±0.3, n=4) (p<0.05). The highest concentration of TUG891 (100 μM) caused ~80% relaxation. After caff/ry treatment, pre-contraction to MCh was maintained but slower, relaxation to salbutamol was reduced while the dilator response to TUG891 was abolished. TUG891 completely prevented MCh-induced calcium oscillations at >1µM.

Discussion. TUG891 has higher efficacy than salbutamol, with bronchodilation mediated via potent inhibition of calcium oscillations, but no effect on calcium sensitivity. The different receptor targets and mechanisms of airway relaxation of TUG891 and salbutamol suggest that TUG891 may be an alternative or adjunct therapy when β2-mediated relaxation is compromised in severe asthma.
Ebselen prevents cigarette smoke-induced endothelial dysfunction in viral-induced exacerbations of COPD.

Kurt Brassington1, Stanley MH Chan2, Aleksandar Dobric3, Simone De Luca4, Huei Jiunn Seow5, Steven Bozinovski6, Stavros Selemidis1, Ross Vlahos1.1 School of Health & Biomedical Sciences, RMIT University1, Melbourne, VIC, Australia.

Introduction. Chronic obstructive pulmonary disease (COPD) is characterised by severe airflow limitation, lung inflammation and significant oxidative stress, largely caused by cigarette smoke (CS) exposure. Globally, COPD is the 4th leading cause of death, with 50% of these patients dying from a cardiovascular event. Annually, patients experience up to 3 acute exacerbations of COPD (AECOPD) from viral and/or bacterial infection, which further increases the risk of mortality by 30%. Systemic inflammation and oxidative stress promote systemic vascular remodeling and atherosclerosis, however, the underlying mechanisms driving cardiovascular comorbidities in AECOPD remain unknown.

Aim. To define the mechanism driving cardiovascular comorbidities in AECOPD and examine the effectiveness of an antioxidant compound ebselen.

Methods. Male BALB/c mice were exposed to either room air (sham) or CS (9 cigarettes/day, 5 days/week) for 8 weeks followed by intranasal inoculation with influenza A virus (Mem71, 1×10^4.5 pfu) and culled 3 and 10-days post-infection. Mice were orally gavaged once daily with ebselen (10mg/kg) or vehicle (5% CM-cellulose) 1 h prior to the initial CS exposure of the day and during the influenza infection period. The thoracic aorta was excised and used for myography or immunohistochemistry. Cumulative concentration-response curves to acetylcholine (ACh) and sodium nitroprusside (SNP) were performed to investigate endothelial and smooth muscle dilator responses.

Results. ACh caused ~90% relaxation of U46619-contracted aorta from sham-exposed mice irrespective of viral infection and ebselen treatment (n=6). However, CS-exposed mice had significantly impaired aortic relaxant responses to ACh (n=8, ~50% Rmax, p<0.0001), which was further impaired following Mem71 infection (n=8, ~35% Rmax, p<0.01). Remarkably, ACh prompted a 90% relaxation in CS+ebselen treated mice irrespective of viral infection (n=7, p<0.0001). SNP caused ~90% maximum relaxation in all aortae, irrespective of CS status, viral infection or ebselen treatment.

Discussion. CS exposure caused significant aortic endothelial dysfunction which was further deteriorated after viral infection. Ebselen prevented the CS-induced endothelial dysfunction irrespective of viral exacerbation, suggesting this novel therapeutic may be crucial in the treatment of cardiovascular comorbidities seen in AECOPD.

Differential activation of human MRGPRX2 by polymyxins and related antibiotics

Jie Ding6, Nithya A. Fernandopulle1, John A. Karas5, Jian Li, Tony Velkov4, Graham A. Mackay1. Dept of Pharmacology & Therapeutics, Univ of Melbourne1, Parkville, VIC; Dept of Microbiology, Monash Univ2, Clayton, VIC, Australia.

Introduction. The emergence of drug-resistant Gram-negative bacteria has led to re-interest in polymyxin B and colistin and novel polymyxin analogues (e.g. nonapeptides and octapeptin) for improved antimicrobial activity. Polymyxins have been previously reported to trigger mast cell activation through an IgE-independent mechanism, with a recent study demonstrating this to be Mas-related G protein-coupled receptor X2 (MRGPRX2)-dependent (Zhan et al., 2019).

Aims. To characterise the ability of novel polymyxin-based antibiotics to activate human mast cells via MRGPRX2.

Methods. We used a HEK293 cell line expressing human MRGPRX2 and the G protein Ga15 and the human mast cell line LAD2 that natively expresses MRGPRX2. Calcium mobilization in response to the polymyxins was measured using Fura2. Degranulation of LAD2 cells was quantified by release of β-hexosaminidase.

Results. Octapeptin C4, polymyxin B and colistin triggered calcium mobilization in MRGPRX2-transfected HEK293 cells with the former being highly potent (Fig 1). No response was observed in non-transfected cells. A similar pattern was observed in LAD2 cells in both Ca2+- mobilisation and degranulation studies. In contrast, polymyxin nonapeptides were far less potent mobilizers of Ca2+ (Fig 1) and failed to induce degranulation in LAD2 cells.

Discussion. Activation of human mast cells by the polymyxins and octapeptin was MRGPRX2-dependent with octapeptin C4 being one of the most potent activators of MRGPRX2 yet described. Thus, compared to the clinically used polymyxins (B and colistin), octapeptin might be more liable to trigger hypersensitivity whilst nonapeptide polymyxins might be less likely to trigger such adverse events. The molecular mechanisms underpinning these differences in polymyxin activation of MRGPRX2 require further investigation to facilitate the discovery of new-generation safer polymyxins.

456

The effect of substance P and its common metabolites on MRGPRX2 activation in human mast cells
Lin Hsin1, Nithya Fernandopulle1, Jie Ding1, Chris Lumb2, Nicholas Veldhuis3, John A. Karas1, Susan E. Northfield1, Graham A. Mackay1. Department of Pharmacology and Therapeutics, The University of Melbourne1, Melbourne, VIC, Australia; Monash Institute of Pharmaceutical Sciences, Monash University2, Melbourne, VIC, Australia.

Introduction. As well as binding to the neurokinin 1 receptor (NK1R), substance P (SP, sequence: RPKPQQFFGLM-NH2) has been shown to activate the Mas-related G protein-coupled receptor X2 (MRGPRX2) receptor on mast cells (MCs), triggering degranulation with the release of inflammatory mediators such as histamine. SP undergoes rapid C-terminal truncation in vivo to generate the major metabolites SP(1-9)-COOH and SP(1-7)-COOH. While the C-terminus of SP has been shown to be critical for NK1R activation, we predicted that the polybasic N-terminus of SP would be key for MRGPRX2 activation.

Aim. To determine if the major metabolites of SP, SP(1-9)-COOH and SP(1-7)-COOH retained activity at MRGPRX2.

Methods. SP-NH2, SP(1-9)-COOH and SP(1-7)-COOH were synthesized by solid-phase peptide synthesis and purified to >95% purity by HPLC. Stably transfected HEK293 cells expressing NK1R or MRGPRX2 and the LAD2 human MC line were used to determine the activity of SP and its metabolites in Ca2+ mobilization (Fura2), degranulation ([β]-hexosaminidase release) and cytokine (CCL2 release) assays.

Results. As expected from prior studies, both metabolites had essentially no activity at NK1R, even at very high concentrations. In contrast, although reduced in comparison to SP, SP(1-9)-COOH remained able to activate MRGPRX2 when measured by Ca2+ mobilization, MC degranulation (Fig 1) and cytokine production. SP(1-7)-COOH however, only retained weak cytokine release activity.

Discussion. Here we show that despite having no activity at NK1R, the major in vivo metabolite of SP, SP(1-9)-COOH, is still able to activate MRGPRX2, with reduced potency compared to intact SP. This suggests that SP(1-9)-COOH, in particular, may play a regulatory role through modulation of MRGPRX2. However, given the relatively low potency of both SP and SP(1-9)-COOH at MRGPRX2, the in vivo relevance of this finding requires further examination.

457

Cigarette smoking does not worsen skeletal muscle contractile function or loss caused by acute viral infection in mice
Kevin Mou1, Stanley MH Chan1, Kurt Brassington1, Aleksandar Dobric1, Simone N. De Luca1, Huei Jiunn Seow1, Ross Vlahos1. School of Health & Biomedical Sciences, RMIT University1, Bundoora, VIC, Australia.

Introduction. Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation that is largely attributed to cigarette smoking (CS). Skeletal muscle wasting is a prevalent comorbidity that affects up to 40% of COPD patients. Muscle wasting is most frequently reported following an episode of viral infection, such an effect would be amplified by chronic CS exposure.

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

Methods. Male BALB/c mice were exposed to either room air (sham) or CS (9 cigarettes per day, 5 days per week) for 8 weeks followed by inoculation with either influenza A virus (IAV; Mem71, 1x104.5 PFU) or diluent (PBS) and culled 3 days post-infection. Muscle function tests were performed, and prime mover muscles of the hind limbs were collected for morphological analyses.

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

Discussion. Acute IAV infection per se specifically impaired muscle function without muscle loss. This suggests that muscle function may be more vulnerable to IAV infection than muscle mass. The lack of an additive effect may imply the involvement of mechanisms other than simple lung inflammation in driving the observed muscle dysfunction.
Expression profiling of specialised pro-resolving receptors in human peripheral blood mononuclear cells (PBMCs) and polymorphonuclear leukocytes (PMNs)

Julia Park¹, Darren M Riddy¹ and Christopher J Langmead¹. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University¹, VIC, Australia;

Introduction. Resolving excessive inflammation and preventing its progression into chronic pathophysiology such as autoimmune diseases is heavily regulated by the actions of specialised pro-resolving mediators (SPMs) and their six cognate G protein-coupled receptors (GPCRs) (Krishnamoorthy et al, 2018). SPM and the SPM-GPCRs exert their effects on PBMCs and PMNs to ultimately drive resolution of inflammation (Serhan & Levy, 2018).

Aims. We aim to construct a comprehensive profiling of the surface protein and gene expression patterns of the six SPM-GPCRs in human PBMCs and PMNs of healthy donors and compare with that of autoimmune patients, to investigate the association between the expression patterns of the receptors and the pathology of the diseases.

Methods. Human PBMCs and PMNs were isolated from whole blood of healthy donors and their surface protein and gene expression of the six SPM-GPCRs were assessed through flow cytometry and quantitative polymerase chain reaction (qPCR), respectively.

Results. Robust surface expression of SPM-GPCRs was observed on both PBMCs and PMNs as supported by the gene expression analysis. However interestingly, the pattern of surface and gene expression did not correlate.

Discussion. Our findings indicate that human PBMCs and PMNs from healthy donors readily express the six SPM-GPCRs and we have established the methods to assess the expression profile in these cells. These results will be compared to that of autoimmune disorder patients, and provide insight on the pathology of the disease and identify potential drug target(s).


Characterisation of chemokine-dependent signalling in monocytes via chemokine GPCRs CCR1 and CCR2

Rina Pokhrel¹, Simon R Foster¹, Cheng Huang¹,², Anup D Shah¹,²,³, Ralf B Schittenhelm¹,², and Martin J Stone¹. Biomedicine Discovery Institute & Dept of Molecular Biology and Biochemistry,¹ Monash Biomedical Proteomics Facility², Monash Bioinformatics Platform³, Monash University, Clayton, VIC, Australia

Introduction. Chemokines are chemoattractant cytokines which interact with G protein-coupled receptors expressed on the surface of leukocytes. They are key regulators of monocyte recruitment, a crucial step in regulation of inflammatory responses at the sites of inflammation. CC chemokine receptors CCR1 and CCR2 are abundantly expressed on monocytes and are potential therapeutic targets in inflammatory diseases including atherosclerosis and rheumatoid arthritis. Blockade of these receptors has been effective in animal models but has failed in clinical trials due to lack of efficacy. A major reason for the failure is the complexity in the chemokine-receptor signalling network.

Aim. To globally characterise the signalling network downstream of activation of robustly activated chemokine receptors in monocytes using signalling assays and phosphoproteomics.

Methods. We carried out well-established cell -signalling assays for chemokines receptors, including chemotaxis (96- well MultiScreen plates, Merck) and ERK phosphorylation (AlphaLISA Surefire Ultra, Perkin Elmer) in monocyte-like THP-1 cells to characterise CCR1- and CCR2- dependent downstream effects after activation with their specific chemokines. We will perform a phosphoproteomics study using data-independent acquisition (DIA) mass spectrometry to quantify changes in phosphopeptide between untreated and CCL5-stimulated THP-1 cells expressing CCR1.

Results. The chemokine CCL5 elicited a concentration-dependent increase in chemotaxis of THP-1 cells with a classical bell-shaped curve and a peak concentration of 10nmol/L. CCL5 elicited robust pERK signalling with EC₅₀ of 1.42 nmol/L. CCL5-dependent signalling was completely inhibited by CCR1 antagonist BX471 (1µmol/L). This was previously performed for CCR2. CCL2 stimulation time course in phosphoproteomics study promoted 460 phosphosites, 329 unique proteins (1-way ANOVA with FDR <0.05) including phosphorylation of CCR1.

Discussion. These findings will provide critical insights into complexity of chemokine receptor signalling cascade. The validation of targeted proteins identified in the chemokine-dependent signalling pathway will result in development of novel therapeutic interventions for overall regulation of monocyte recruitment.
Involvement of P-glycoprotein (ABCB1) in the export of amyloid-beta from the Alzheimer’s brain

Amanda B Chai, Richard Callaghan, Ingrid C Gelissen. School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2006, Australia; Research School of Biology and Medical School, Australian National University, Canberra, ACT 2601, Australia.

Introduction. Defective clearance mechanisms in the Alzheimer’s brain lead to the accumulation of amyloid-β (Aβ) peptides, in particular Aβ_{40} and Aβ_{42}. These peptides form characteristic plaques and toxic soluble oligomers that contribute to impaired synaptic function, memory loss, neurodegeneration, and cognitive decline. The role of P-glycoprotein (P-gp or ABCB1) in exporting Aβ across the blood brain barrier is well-established, however little is known about how these hydrophobic peptides, initially produced in neurons, are first released into the extracellular space.

Aims. To assess whether P-gp is expressed, active, and involved in the export of Aβ from neurons.

Methods. We measured P-gp protein expression and activity using Western blotting and calcein-AM assays respectively. CHO-APP and SK-N-SH cells were treated with the P-gp inhibitors verapamil and nicardipine, then Aβ_{40} and Aβ_{42} secretion into cell media was quantified by ELISA.

Results. P-gp protein expression was detected in human neuroblastoma cell lines and primary rodent brain derived neurons. P-gp was shown to be active in SK-N-SH cells, using the Calcein-AM assay. Chemical inhibition of P-gp reduced export of Aβ_{40} and Aβ_{42} from CHO-APP and SK-N-SH cells in a concentration-dependent manner.

Discussion. Data show that Aβ can be transported by P-gp, and inhibition of P-gp impairs export of these peptides out of neurons. These results present a paradigm shift in thinking of what drives export of these peptides from neurons and what impact a reduction in P-gp over time may have on markers of neurodegeneration or Alzheimer’s symptoms. Discerning the cellular clearance mechanisms of Aβ will provide significant contributions to our understanding of the pathophysiology and treatment of Alzheimer’s disease.


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

Natasha C Dale, Elizabeth KM Johnstone, Kevin DG Pfleger. Mol Endocrinol and Pharmacol, Harry Perkins Inst of Med Res, Nedlands, WA, Australia; Centre for Med Res, Univ of Western Australia, Crawley, WA, Australia; Aust Res Council Centre for Personalised Therapeutics Technologies, Australia; Dimerix Limited, Nedlands, WA, Australia.

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

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

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

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

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

Ivacaftor, a cystic fibrosis modulator drug, in pregnancy and lactation: entry into the developing brain and lung

Fiona Qiu1, Elena K Schneider-Futschik1, Mark D Habgood1, Yifan Huang1, Sam Toll1, Katarzyna M Dziegielewsk1, Norman R Saunders1. Dept of Pharmacology & Therapeutics, The University of Melbourne1, Parkville, VIC, Australia

Introduction. With the rapid expansion of therapeutic modulators of cystic fibrosis transmembrane conductance regulator (including ivacaftor), the life expectancy of cystic fibrosis (CF) patients has increased substantially, enabling more CF women to reach child-bearing age (Heltshe et al, 2017). However, it is uncertain how safe is long-term use of ivacaftor during pregnancy and breastfeeding for the fetus and newborn, especially for their developing brain.

Aims. 1) To determine transfer of ivacaftor across placenta in pregnancy and breast tissue during lactation. 2) To investigate entry of ivacaftor into brain and lungs of pre- and postnatal rats following acute or long-term exposure.

Methods. Pregnant Sprague Dawley rats at embryonic day (E) 19 were administered a single ip injection of ivacaftor at a clinically relevant dose of 40 mg/kg tracer with [3H] ivacaftor. Following terminal anaesthesia (ip urethane 2.5 g/kg), blood samples from individual pups were serially collected along with time-matched maternal blood samples and radioactivity was measured by liquid scintillation counting. Postnatal animals were either administered a single ip injection of radiolabelled ivacaftor or exposed to the drug via milk from an orally treated dam over 4-14 days. Blood, brain and lung samples were analysed using liquid scintillation or LC-MS.

Results. 1) Placental transfer of ivacaftor from maternal to fetal plasma was around 30%. In lactating dams, the average concentration of ivacaftor in pup plasma was about 40% of the maternal plasma concentration. 2) In acutely exposed postnatal pups, the average tissue/plasma concentration ratios were around 2% and 330% for brain and lungs respectively. Following 4 days of exposure, the ratios increased in the brain to over 20% but decreased in lungs to about 180%. With longer exposure these ratios decreased in all tissues by day 14.

Discussion. Fetal and postnatal rats are exposed to maternally administered ivacaftor via placental and milk transfer. Entry of ivacaftor into the brain was much lower than into lungs at all ages. These data may suggest the possibility of babies facing therapeutic level of ivacaftor that preferentially enters their lungs. Further investigation is required to determine the exact mechanism that allows for entry of ivacaftor into the brain and lungs at different developmental ages, and the effects of ivacaftor in the developing human brain.


Can monitoring clozapine levels reduce the occurrence of peripheral ADRs?

Madeleine SA Tan1, Faraz Honarpvar2, James R Falconer1, Harendra S Parekh1, Preeti Pandey1, Dan J Siskind1,3

School of Pharmacy, The University of Queensland2, QLD Australia; School of Medicine, The University of Queensland2, QLD, Australia; Metro South Addiction and Mental Health Service, Princess Alexandra Hospital3, QLD Australia.

Introduction. Clozapine is the most effective antipsychotic for treatment-refractory schizophrenia for reducing positive psychotic symptoms. It has a lower rate of drug discontinuation compared to other second-generation antipsychotics and is associated with a reduction in overall mortality. In spite of this, clozapine remains underutilized due to adverse drug reactions (ADRs) such as weight gain, hypersalivation and constipation. Individual ADRs may be associated with clozapine levels.

Information on the relationship between clozapine levels and ADRs can help inform clinicians and patients in making choices about optimising clozapine dose to balance therapeutic effect and ADRs.

Aims. The aim of this systematic review is to determine the correlation between clozapine levels and ADRs, and to undertake pairwise meta-analyses, where possible.

Methods. Studies were searched from four electronic databases (PubMed, EMBASE, PsycINFO and CINAHL) from inception to 12 June 2020. Studies were included if they had adult patients (≥16 years), provided data on steady-state trough clozapine levels, and reported on clozapine associated ADRs. Pregnant women, case reports and series were excluded.

Results. A statistically significant correlation was found for clozapine serum levels and triglycerides (n=70; r=0.303, 95% CI 0.0119 to 0.546, p=0.042, I²=22.9%), heart rate (n=137; r=0.269, 95% CI 0.0918 to 0.486, p=0.035, I²=58.4%), and overall combined ADRs (n=160; r=0.264, 95% CI 0.110 to 0.405, p=0.001, I²=0%), but not for absolute neutrophil count (n=223; r=-0.164, 95% CI -0.529 to 0.253, p=0.444, I²=86.3%) or total white cell count (n=189; r=0.0176, 95% CI -0.203 to 0.237, p=0.878, I²=56.1%). Interestingly, norclozapine serum levels was found to be statistically correlated to triglycerides (n=120; r=0.211, 95% CI 0.0305 to 0.378, p=0.022, I²=0%), total cholesterol (n=120; r=0.272, 95% CI 0.0948 to 0.432, p=0.003, I²=0%), and weight gain (n=118; r=0.208, 95% CI 0.0261 to 0.377, p=0.025, I²=0%).

Discussion. Clozapine levels may be correlated to metabolic abnormalities and increased HR. However, a true correlation can be difficult to interpret clinically using observational studies. Further prospective, randomized studies are needed to identify the cause-effect relationship of clozapine level and peripheral ADRs.
464

Entry of valproate and lamotrigine into the developing brain
Samuel J Toll1, Norman R Saunders1, Mark D Habgood1, Katarzyna M Dziegielewska1, Yifan Huang1, Fiona Qiu1. Dept of Pharmacol1, Univ of Melbourne, Parkville, VIC.

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

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

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

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

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


465

Male-female differences in the effects of age on mouse activities of daily living measured using an automated behavioural classification
Trang Tran1,3, John Mach1,2,3, Gizem Gemikonakli1,3, Harry Wu1,3, Heather Allore4, Susan Howlett5, Christopher Little1,6 & Sarah N Hilmer1,2,3. Lab of Ageing and Pharmacology, Kolling Institute, Sydney, NSW, Australia1; Clinical Pharmacology and Ageing, Royal North Shore Hosp, NSW, Australia2; Faculty of Medicine and Health, Univ of Sydney, Sydney, NSW, Australia3; Dept of Biostatistics, Yale Univ, Connecticut, USA4; Dalhousie Univ, Halifax, NS, Canada5; Raymond Purves Bone and Joint Research Lab, Kolling Institute, Sydney, NSW, Australia6.

Introduction. Activities of daily living (ADLs) are fundamental self-care tasks that are routinely performed by individuals, and are important global health outcomes. Independence in ADLs differs with age and sex in humans. Laboratory animals are often used to study pharmacological and toxicological effects. However, the impacts of age, sex and the interaction between these two factors on murine routine activities have not been well characterised.

Aims. Using a mouse model, we aimed to study how age and sex affect murine ADLs over 23 hours.

Methods. Young (2.5 months) and old (21.5 months) C57BL/6 male and female mice were assessed using an automated behavioural recording machine – the Laboratory Animal Behaviour Observation, Registration, and Analysis System for 23 hours. Mice were individually caged for recording of ADLs including distance travelled, mean gait speed, and the durations of locomotion, rearing, climbing, grooming, immobility, eating and drinking.

Results. Compared to young mice of the same sex, old mice travelled significantly shorter distances with slower gait speed and had shorter durations of locomotion, rearing, climbing and immobility, particularly during the dark cycle between 7pm-7am. Compared to old males, old females reared more during the light cycle between 11am-7pm (p<0.05). Young female mice spent significantly more time climbing than young males. Significant age-sex interactions were detected for rearing and climbing, in which females did not decline as much in old age as males. Within the same sex, old mice groomed more than young mice (p<0.05). No differences were observed with age and sex for the duration of drinking and eating.

Discussion. Our results suggest that in mice, old age may decrease exploratory activities but increase grooming. The age-related decline varies between sexes and tends to be more severe in males. This assessment should be a useful translatable outcome to study how different interventions affect ADLs in rodents of different ages and sexes.
466

Self-nanomicellizing solid dispersion of USA612: Solubility improvement

Fatima Abid1, Ankit Parikh1, Stephen W Page2, Sanjay Garg1, Clinical and Health Sciences, University of South Australia3, Adelaide, SA, Australia; Neoculi Pty Ltd2, Burwood, VIC, Australia.

Introduction. Despite broad-spectrum antimicrobial activities of USA612 including antibacterial, antifungal, and antiviral activities, the translation of USA612 into a useful therapeutic is still limited due to its poor aqueous solubility (≤40 µg/mL). To overcome this formulation challenge and enhance its aqueous solubility, self-nanomicellizing solid dispersion (SNMSD) strategy was used to develop a novel USA612 formulation (NUF).

Aims. Development of NUF using SNMSD strategy for the enhancement of its aqueous solubility.

Methods. Since USA612 does not have a chromophore, a new analytical method was developed using HPLC Refractive Index (RI) detectors. Based on the literature review, three polymers (Soluplus, HPMC- ASLG and HPMC-ASMG) were selected for their potential to improve the solubility with the drug/polymer ratio 1:5. The solvent evaporation technique was used to prepare three SNMSDs. The solubility was evaluated at predetermined time intervals using our developed analytical method. The NUF was characterized using differential scanning calorimetry, X-ray diffraction, scanning electron microscopy and Fourier transform infrared spectroscopy. Besides, its self-micellizing properties were assessed after dissolving in aqueous media for particle size, zeta potential, loading ability, and morphology through transmission electron microscopy analysis.

Results. A simple, reproducible and rapid chromatographic methodology has been developed and applied successfully for the determination of USA612 from aqueous media. The results showed that the linear range for USA612 was 100-500 µg/mL with the squared correlation coefficients (R²) being 0.9992. The optimised NUF showed significantly improved aqueous solubility of >1000 µg/mL in PBS pH 7.4. The amorphization, hydrogen bonding interaction, and micellization could have played a vital role in the improvement of the solubility profile of USA612.

Discussion. The results demonstrated that SNMSD system could serve as a promising strategy to improve USA612 solubility and NUF could be a potential candidate for the treatment of infectious diseases.

467

Does co-administering whole and crushed paracetamol with Gloup alter drug dissolution profile in vitro?

Marwa A. Malouh1, Julie A.Y. Cichero1,2, Esther T.L. Lau1,2, Lisa M. Nissen1,2, Chandramouli Radhakrishnan1, Kathryn J. Steadman1,2. School of Pharmacy, The University of Queensland1, Brisbane, Qld, Australia. School of Clinical Sciences, Queensland University of Technology2, Brisbane, Qld, Australia.

Introduction. Gloup is designed to facilitate swallowing of tablets and capsules whole for those who find it difficult. In practice, Gloup is used with crushed tablets as well as whole. We have previously shown that dissolution of crushed tablets co-administered with thickened fluids can be significantly delayed.

Aim. To evaluate the effect of co-administering whole and crushed tablets with Gloup on drug dissolution.

Methods. The dissolution of whole and crushed paracetamol tablets mixed with two IDDSI (International Dysphagia Diet Standardisation Initiative) level 3 swallowing medication lubricants (Gloup Low Sugar, Gloup Original strawberry/banana) was tested in simulated gastric fluid. Comparisons were made with water, and water thickened to IDDSI level 3 (liquidised/moderately thick) using a xanthan gum product (Easythick Advanced).

Results. Dissolution of immediate release paracetamol tablets is very fast whether crushed or whole. When co-administered with Gloup dissolution of whole was slightly delayed but reached 85% by 30 to 60 min. Dissolution of crushed tablets was affected more strongly than whole tablets, as 50-70% was dissolved by 30 minutes, 85% dissolution was reached after 80 to 150 min, and with little difference between Gloup and water thickened with xanthan gum.

Discussion. There is a delay in paracetamol dissolution when co-administered with Gloup instead of water, and this delay is increased if tablets are crushed. However, it is important to bear in mind that salivary mixing and shear forces exerted on the Gloup during oral preparation and swallowing are not accounted for by the simple dissolution test, so more research is needed before any conclusions around clinical relevance can be made.
Co-amorphous kanamycin-amino acid spray-dried inhalable particles: the influence of feed concentration in achieving high aerosolization

Bishal Raj Adhikari1, Keith C. Gordon2, Shyamal C. Das1. School of Pharmacy, University of Otago2, Dunedin, NZ; Department of Chemistry, University of Otago1, Dunedin, NZ.

Introduction. Co-amorphization of kanamycin with amino acids by co-spray drying is known to improve aerosolization of kanamycin. However, various spray drying processing factors may influence the aerosol performance of these co-amorphous systems.

Aims. This study aimed to assess the influence of feed concentration on aerosolization for kanamycin-amino acid co-amorphous powders using kanamycin-valine (KV) as a model system.

Methods. Using 0.2% and 0.4% w/v feed solutions, KV02 and KV04 formulations were prepared by spray-drying kanamycin and valine in 1:1 molar ratio, and K02 and K04 by spray-drying kanamycin alone. All formulations were characterized using X-ray diffraction (XRD), Infrared (IR) spectroscopy, Thermogravimetric Analyzer (TGA), Differential Scanning Calorimetry (DSC), and Scanning Electron Microscopy (SEM). The in-vitro aerosol performance was assessed using Next Generation Impactor (NGI).

Results. The average particle sizes of the KV02 and KV04 were around 0.9 and 1.2 µm. All co-spray dried particles were amorphous determined by XRD. Further the co-amorphicity of the powders was confirmed using DSC. Although both KV02 and KV04 showed higher ED, improvement in FPF was observed for only KV02. For example, the emitted dose (ED) of the K02 and K04 were 71.1% and 66.9%, and the ED of kanamycin from KV02 and KV04 were 78.8% and 77.5%, respectively. In contrast, the Fine Particle Fraction (FPF) of kanamycin significantly increased for kanamycin-valine formulations at 0.2% feed concentration, e.g., 70% for K02 vs 78% for KV02 (p<0.05) while the FPF of kanamycin did not change for formulations at 0.4% feed concentration, e.g., 73% for both K04 and KV04.

Discussion. The similarity in ED and the difference in FPF between KV02 and KV04 suggest that although the co-amorphous powders exit the device, the powders disperse into primary particles and smaller aggregates whose size ultimately define particle deposition behaviour. While further studies are undergoing to reveal the exact mechanism, it seems that aerosolization behaviour is influenced by feed concentration for kanamycin-amino acid co-amorphous systems.

Characterization of Novel Inulin hydrogels loaded with 5-fluorouracil for colon delivery

Franklin Afinjuomo1, Paris Fouladian1, Yunmei Song1, Ankit Parikh1, Sanjay Garg1. Clinical and Health Sciences, University of South Australia, Adelaide, SA, Australia.

Introduction. A significant challenge in the drug treatment of colon cancer is the optimization of drug delivery as well as how to avoid severe systemic side effects during chemotherapy. For instance, 5-fluorouracil (5-FU) is currently administered by intravenous route. This limits the clinical application of 5-FU due to unwanted systemic side effects and off-target problems. To address this limitation, there is an urgent need for the development of a suitable drug delivery platform which can help to reduce the toxicity of 5-FU by providing targeted, localized and sustained drug release to the colon.

Aims. To characterize smart hydrogels loaded with 5-FU for colon targeted delivery

Methods. Inulin hydrogels were prepared by the esterification reaction by crosslinking raw inulin with pyromellitic dianhydride (PMDA) using triethylamine as a catalyst[1] followed by loading with 5-FU using the swelling method. The physicochemical characterization of the drug-loaded 5-FU gels was determined using different techniques such as Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), Scanning electron microscopy (SEM), in-vitro release, degradation and cytotoxicity studies.

Results/Discussion. FTIR was used to confirmed the encapsulation of 5-FU with new peaks at 3071, 1246, 1433, 750 cm⁻¹. XRD confirmed the disappearance of 5-FU crystalline peaks in the formulation. SEM showed the change in surface morphology and the encapsulation of 5-FU within the pores (Figure 1). HPLC results confirmed encapsulation of 5-FU with loading between 8.2-18.0 % depending on the ratio of PMDA crosslinker. The drug release was characterized by both burst and control release in the pH conditions of the gastrointestinal tract. Furthermore, 5-FU loaded gels are degradable with the use of inulinase and MTT assay shows a dose-dependent efficacy against HCT116 from the 5-FU loaded hydrogels. These preliminary results make the hydrogels a promising platform for the localized delivery of 5-FU to the colon.

470

**Glycine-Proline-Glutamate loaded bi ligand niosomal delivery system interactions on Cell Models**

Murad A. Gailani1, Naibo Yin1, Jingyuan Wen1. School of Pharmacy, University of Auckland1, Auckland, New Zealand.

Introduction. Glycine-Proline-Glutamate (GPE) is a neuroprotective peptide with a dose-dependent and receptor mediated mechanism leading to downregulation of inflammation, promotion of astrocytosis, and inhibition of apoptosis, beneficial in many neurodegenerative diseases. Oral and intravenous administration of GPE has limited transport across the blood-brain-barrier (BBB) due to its hydrophilicity and susceptibility to enzymatical degradation in the body. Encapsulation into a bi ligand niosomal delivery system can improve both the stability and penetration of GPE.

Aims. To evaluate the interaction of GPE loaded bi-ligand niosomal delivery system on Rat Brain Endothelial (RBMVE) cells mimicking the BBB.

Methods. The niosomes were fabricated using thin-film hydration technique by mixing surfactant, dicetyl phosphate, poly-l-arginine-conjugated polyethylene glycol and cholesterol dissolved in a mixture of organic solvents. The RI7 ligand conjugate is then incubated with niosomes overnight to form the bi-ligand niosomal delivery system. Cell viability of GPE between 5-1000 μM was determined by MTT assay. Cellular uptake of GPE and its mechanism on Caco-2 cells were also investigated in the absence and presence of the niosomes.

Results. GPE loaded bi-ligand niosomal delivery system was successfully fabricated and evaluated on RBMVE cells, showing no significant cytotoxicity at low concentrations and improved uptake and transport in the presence of the bi-ligand niosomal system.

Discussion. The niosomal delivery system and its individual constituents are not toxic to cells and have improved cellular uptake of the drug delivery system into the cells when compared against free drug suggests this niosomal delivery system has potential for neuropeptide delivery across the BBB.

471

**Hand sanitizer for hand hygiene during COVID-19 in New Zealand: A response to the community’s need by staff and students of the School of Pharmacy, University of Otago**

Shyamal C. Das, Tushar Saha, Rishi Shah, Nicole Wood, Bishal Adhikari, Rakesh Bastola, Prakash Khadka, Carlo A. Marra; School of Pharmacy, University of Otago, Dunedin, NZ.

Introduction: Hand sanitizer is an essential commodity to maintain hand hygiene and to prevent the spread of SARS-CoV-2, the causative virus of COVID-19, as well as other microorganisms. During this COVID-19 pandemic, the demand for hand sanitizer has increased dramatically worldwide, including New Zealand (NZ).

Aims: The aim of this project is to describe how the University of Otago School of Pharmacy contributed to the community need with hand sanitizer during COVID-19.

Methods: The ‘Dr Das Research Group’ was formed and registered with the Ministry of Primary Industries to prepare hand sanitizer voluntarily at the School of Pharmacy, University of Otago (UoO). This group produced alcohol-based hand sanitizer as prescribed by the World Health Organization, following all health and safety and regulatory guidelines. The product was distributed to essential workers during NZ’s lockdown in March-May, 2020 through the University’s Emergency Response team.

Results: Starting just three days before the lockdown, and working during the lockdown, 1200 litres of hand sanitizer were produced without any automation. It was used by the essential services of the UoO’s Dunedin campus, local Civil Defence, the Dunedin and Canterbury Police, Fire and Emergency, St John Ambulance Service, Driving Miss Daisy Dunedin and a Māori Health provider during lockdown. In addition, Dr Das has been consulted by many health providers in NZ for advice and has inspired many universities, organizations and individuals to produce their own hand sanitizer.

Discussion: The skills necessary for the preparation of hand sanitizer are universal for pharmaceutical scientists giving the opportunity for the School of Pharmacy to make a contribution to society during lockdown. This project had a positive impact on the community by taking pressure off commercial suppliers, freeing up capacity for the general public, and minimizing risk of front line workers. The project has attracted significant media attention locally and internationally.
Novel functionalized mesoporous silica nanoparticles targeting estrogen receptor over-regulated breast cancer

Candace M Day1, Martin J Sweetman1, Shane M Hickey1, Yunmei Song1, Yongjun Liu2, Na Zhang2, Sally E Plush1, Sanjay Garg1, University of South Australia, Adelaide, SA, Australia, School of Pharmaceutical Science1, Shandong, Ji’nan, China

Introduction. Conventional chemotherapy for breast cancer (BC) destroys both healthy and cancerous cells. To address this issue, a novel drug delivery system (DDS) based on mesoporous silica nanoparticles (MSNs) was fabricated to selectively deliver incorporated anticancer drugs to BC. The inorganic fluorophore Rezolve-L1 (REZ-L1) was trialled as an encapsulated material to provide the proof of concept.

Aims. Successfully synthesize and functionalize MSNs with active targeting ligands for enhanced selectivity to BC. REZ-L1 molecules were encapsulated within the mesopores with high capacity. REZ-L1-loaded MSNs achieved active endocytosis into BC cell lines.

Methods. Surface functionalization was conducted via click-chemistry. REZ-L1 molecules were loaded on to MSNs used solvent immersion technique. Encapsulation and loading capacity were determined via UV-Vis, from varied concentrations of REZ-L1 solutions determined through the Beer Lambert equation.

Results. The system achieved a grafting ratio of functionalities of approximately 29%. Rezolve-L1 was successfully loaded with a maximal encapsulation efficacy pf 65% and a REZ-L1 loading capacity ranging from 10 to 40% (w/w).

Discussion. The functionalized MSNs were successfully designed and developed for the active targeted delivery of REZ-L1 to BC. This novel DDS offers valuable applications in breast cancer therapeutics and diagnostics.


A Novel Rat Cervical Lymph Cannulation Method to Evaluate the Lymphatic Clearance of Therapeutics from the Brain

Thu A Hoang1, Gracia1, Enyuan Cao1, Joseph A Nicolazzo1, Natalie L Trevaskis1. Drug Deliv, Disp and Dynamics, Monash Univ1, Parkville, VIC, Australia.

Introduction. Several recent studies have demonstrated the drainage of fluid, immune cells, fluorescent tracers and dyes along meningeal and cervical lymphatic vessels following injection into the brain. However, no previous studies have evaluated the potential role of the lymphatics in the clearance of therapeutics from the brain.

Aim. 1) To develop a new method to cannulate and collect cervical lymph in rats. 2) To determine the lymphatic clearance of therapeutics from the brain in rats.

Methods. Sprague-Dawley rats were anaesthetised with 1.5-5% inhaled isoflurane then cannulated/ligated at the carotid artery +/- at the cervical lymph duct. Rats were administered via direct injection into the brain parenchyma with 14C-ibuprofen (a small molecule, non-lipophilic drug) or 3H-albumin (a model for large protein therapeutics) at a rate of 0.5µl/min over 16 min. Blood and lymph samples were collected for up to 8 h following dosing and brain tissue was collected at 8 h. Samples were subsequently analysed for radioactivity levels via scintillation counting.

Results and Discussion. In rats administered 14C-ibuprofen into the brain, plasma concentrations of 14C-ibuprofen over time were higher in lymph-ligated rats than in lymph-intact rats (plasma AUC 6.0 ± 0.6 versus 2.4 ± 0.7 %dose.h/ml, respectively). This suggests that ibuprofen is cleared from the brain across the blood-brain barrier and has minimal lymphatic clearance. Following injection of 3H-albumin into the brain, lymph:plasma concentration ratios of 3H-albumin were very high (up to 54:1). Plasma concentrations over time were not significantly different between lymph-intact and lymph-ligated groups, but were lower in lymph-cannulated rats (plasma AUC 3.3 ± 1.0, 3.1 ± 0.9 and 1.1 ± 0.5 %dose.h/ml, respectively). Together these results indicate that albumin is transported from the brain via the lymphatics.

Conclusion. A cervical lymph cannulation method has been developed for the first time in rats. The lymphatics contribute to the brain clearance of the protein albumin, but not for the small molecule therapeutic ibuprofen. Future studies will evaluate whether centrally-acting drugs also undergo lymphatic elimination from the brain as this has the potential to significantly influence drug accumulation in the brain and thus drug efficacy and toxicity.
474

Triple negative breast cancer: Screening for the invasion amplifying cAMP-calcium feedforward loop mechanism
Terrance Lam1, Erica K Sloan1,2,3, Michelle L Halls1. Drug Disc Biol Theme, Monash Inst Pharm Scie1, Monash University, Parkville, VIC, Australia; Cousins Center, UCLA Semel Inst Neurosci and Human Behav and Jonsson Comprehensive Cancer Center, University of California Los Angeles2, California, USA; Div Cancer Surgery, Peter MacCallum Cancer Centre3, East Melbourne, VIC, Australia.

Introduction. Previously, we identified a cAMP-calcium (Ca\textsuperscript{2+}) feedforward loop mechanism in the highly metastatic triple negative breast cancer (TNBC) tumour cell line MDA-MB-231\textsuperscript{HM} (Pon et al, 2016). This mechanism facilitates the dynamic interplay between cAMP and Ca\textsuperscript{2+} second messenger systems following β2 adrenoceptor activation, to further amplify both signals. Activation of this mechanism facilitates accelerated invasion in MDA-MB-231\textsuperscript{HM} cells.

Aims. To determine the commonality of the β2-adrenoceptor mediated feedforward mechanism amongst a panel of TNBC tumour cell lines and to establish its role in regulating cellular invasion.

Methods. Formoterol was used to activate the endogenously expressed β2-adrenoceptor. Receptor signalling was measured using cAMP accumulation and Ca\textsuperscript{2+} mobilisation assays in the presence of various inhibitors: adenylyl cyclase (2',3'-dideoxyadenosine), G\textsubscript{αi/o} (pertussis toxin), G\textsubscript{βγ} (gallein), protein kinase A (KT5720), exchange protein activated by cAMP (E划分-09), protein kinase C (GF109203X), and Ca\textsuperscript{2+} chelator (BAPTA-AM). 3D cellular invasion was assessed using microscopy.

Results. Preliminary screening identified three TNBC cell lines which possess elevated cAMP and increased intracellular Ca\textsuperscript{2+} in response to β2-adrenoceptor stimulation by formoterol; MDA-MB-453 (pEC\textsubscript{50} cAMP 8.42 ± 0.25, Ca\textsuperscript{2+} 7.74 ± 0.27), HCC1806 (pEC\textsubscript{50} cAMP 8.39 ± 0.04, Ca\textsuperscript{2+} 8.70 ± 0.89), HCC1395 (pEC\textsubscript{50}cAMP 7.97 ± 0.23, Ca\textsuperscript{2+} 8.76 ± 0.51). These results provide preliminary evidence for a cAMP/Ca\textsuperscript{2+} feedforward loop mechanism within these cell lines. Inhibitors were used to delineate any interaction between the cAMP and Ca\textsuperscript{2+} signalling pathways, and to confirm whether activation of the cAMP/Ca\textsuperscript{2+} feedforward loop was required to accelerate invasion.

Discussion. The β2-adrenoceptor can accelerate breast cancer progression in response to stress. The feedforward loop may provide strategies to more specifically target this GPCR in order to slow cellular invasion and metastasis.


475

An effective HPTLC method for quality standardisation of Australian propolis
George Q Li1, Jim Zou2, Chun Guang Li1*,
NICM Health Research Institute1, Western Sydney University, NSW 2747, Australia; Jim’s Bee Products2, Young, NSW 2594, Australia

Introduction. The quality standard of Australian propolis is lacking, which limits the development of the Australian authenticate propolis.

Aims. the aim of this study is to develop an effective method and compare propolis from various sources to determine the variation of chemical profile of Australian propolis.

Methods. Several propolis products and raw materials were collected from various regions including Chinese, New Zealand, Brazilian, and Australia. The raw materials were extracted with ethanol and products diluted with ethanol and applied to HPTLC together with reference compounds. The mobile phase was consisted of toluene-ethyl acetate-formic acid. The chemical profile with or without anisaldehyde - sulfuric acid colour derivatisation was observed by UV light of 254 and 366 nm wavelength to detect the phenolic acids and flavonoids for UV absorbance and fluorescent.

Results. Phenolic compounds and flavonoids showed reproducible different colours under different chromatographic conditions, and samples from different regions had a similar pattern. Fig 1 was a HPTLC chromatograms of ethanolic extracts of propolis from different sources, under UV 366 nm after derivatisation and showed Australian propolis and Brazilian propolis had multiple yellow bands, while Chinese propolis had multiple light blue bands. Products in Australian market labelled Australian propolis were like Chinese propolis, and one raw Chinese material was adulterated by quercetin.

Discussion. The results indicate HPTLC method is rapid, very informative and efficient in comparing the fingerprint of propolis sources. Further work to collect sufficient representative Australian samples are warranted to determine the variation and quality standards of Australian propolis.
The expression and function of fatty acid-binding proteins in microglia: what potential role do they play in the uptake of docosahexaenoic acid?

Yi Ling Low\textsuperscript{1}, Yijun Pan\textsuperscript{1}, Jennifer L Short\textsuperscript{2}, Joseph A Nicolazzo\textsuperscript{1}. \textsuperscript{1}Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences\textsuperscript{1}, Parkville, VIC, Australia. \textsuperscript{2}Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia.

Introduction. The overactivation of microglia leads to the excessive release of proinflammatory mediators, causing prolonged neuroinflammation, which is detrimental to brain health. Docosahexaenoic acid (DHA) has been shown to alleviate neuroinflammation by inhibiting the release of proinflammatory mediators from microglia. Therefore, the uptake of DHA into microglia is essential for reducing neuroinflammation. Cytoplasmic carrier proteins, fatty acid-binding proteins (FABPs), are involved in DHA trafficking in other cell types.

Aims. This study focused on screening whether various FABP isoforms are expressed in microglia, and whether they are involved in the uptake of DHA into microglia.

Methods. Using immortalised mouse microglia (BV-2) cells, quantitative reverse-transcriptase real-time polymerase chain reaction and western blotting were used to quantitatively determine the mRNA and protein levels of the 10 known FABP isoforms.

Results. FABP3, FABP4, and FABP5 were expressed at both the mRNA and protein level in BV-2 cells. A genetic knockdown approach was then taken to investigate the involvement of these highly expressed FABP isoforms in the microglial uptake of DHA-d\textsubscript{5}. Interestingly, following 77.5–92.3\% (at mRNA level) and 45.4–81.7\% (at protein level) knockdown of FABP3, FABP4, and FABP5 at 48 hours, no changes in DHA-d\textsubscript{5} uptake into microglia was observed at 2 min.

Discussion. This suggested the involvement of other microglial DHA uptake mechanisms, such as the possible involvement of membrane transporters like fatty acid transport proteins (FATPs).

Copper complexes modulate the expression and function of P-glycoprotein at the blood-brain barrier

Jae Pyun\textsuperscript{1}, Celeste Mawal\textsuperscript{2}, Ashely I Bush\textsuperscript{2}, Jennifer L Short\textsuperscript{3}, Joseph A Nicolazzo\textsuperscript{1}. Drug Delivery, Disposition and Dynamics\textsuperscript{1}, Drug Discovery Biology\textsuperscript{3}, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia, Florey Institute of Neuroscience and Mental Health\textsuperscript{2}, Melbourne, VIC, Australia.

Introduction. Efflux transporters expressed on the luminal surface of brain endothelial cells act as biochemical barriers to xenobiotic insult and regulate the transport of molecules across the blood-brain barrier (BBB). P-glycoprotein (P-gp) is one of the main efflux transporters involved in the hindrance to central nervous system (CNS) drug delivery. P-gp also plays a major role in the transport of endogenous molecules such as amyloid beta (A\textbeta) from the brain into the systemic circulation. The expression of P-gp is decreased in people with Alzheimer’s disease (AD) which is suspected to decrease the clearance of neurotoxic A\textbeta from the brain parenchyma. Biometals such as copper (Cu\textsuperscript{2+}), have been shown to be important for the regulation of many signalling pathways in neurons and these pathways are linked to P-gp expression. However, whether Cu\textsuperscript{2+} or other biometals are involved in the regulation of P-gp is yet unknown.

Aims. To increase brain endothelial levels of Cu\textsuperscript{2+} through the use of bis(thiosemicarbazone) (BTSC) complexes, Cu(ATSM) and Cu(GTSM), and assess the impact on P-gp expression and function at the BBB.

Methods. Expression of P-gp at the protein level and transcript level (mdr1) in immortalised human brain endothelial (hCMEC/D3) cells were quantified by Western blot and quantitative polymerase chain reaction respectively following treatment with 25 – 250 nM range of Cu(BTSC) for 24 and 48 h. P-gp function was assessed through the uptake of a fluorescent P-gp substrate, rhodamine 123. Intracellular Cu\textsuperscript{2+} levels were quantified following treatment with the Cu(BTSC)s by inductively coupled plasma mass spectrometry.

Results. Relative to control, Cu(ATSM) significantly enhanced P-gp protein expression 2.0-fold, mdr1 expression 1.5-fold and P-gp function by 29.2\% at the 100 nM concentration. In contrast, a 48 h treatment with Cu(GTSM) diminished P-gp expression at both protein (0.5-fold) and mRNA level (0.6-fold) leading to a reduction in P-gp function by 105.4\%. Both Cu(ATSM) and Cu(GTSM) were found to increase cytosolic Cu\textsuperscript{2+}.

Discussion. The upregulation of P-gp expression and function was unexpected as Cu(GTSM) was thought to release Cu\textsuperscript{2+} whereas Cu(ATSM) has previously been shown to only release Cu\textsuperscript{2+} under hypoxic conditions. Thus, it may indicate that P-gp expression is mediated by a Cu\textsuperscript{2+} independent mechanism which requires further investigation.
Method Development and Validation for Determination of Sucralfate in Marketed tablets by HPLC-ELSD
Yunmei Song1, Ruixiu Li1, Thabata Muta1, Stephen W. Page2, Franklin Afinjuomo1, Ankit Parikh1, Sanjay Garg1
1 Clinical and Health Sciences, University of South Australia, Adelaide, SA 5000, Australia; 2 Advanced Veterinary Therapeutics, Newtown, NSW 2042 Australia

Introduction. The currently reported analytical methods for sucralfate include High-performance liquid chromatography with a Refractive Index detector (HPLC-RI)[1] and HPLC-UV[2], but there is no publication of a chromatographic method with an HPLC using evaporative light scattering detector (HPLC-ELSD) for the quantitative determination of sucralfate. Compared to RI and UV detection, ELSD is less sensitive to temperature and flow-rate variability, has a higher order of magnitude and the response is independent of solvents[3]. These advantages make ELSD a promising detector in the application of determination of sucralfate. Therefore, we developed and validated a simple, rapid, sensitive, and precise HPLC-ELSD method for the determination of sucralfate under the requirement of the ICH Guideline[4].

Method. An analytical method with an HPLC-ELSD was established and validated to determine sucralfate. The method was performed on a column of Luna® 100Å NH2(4.6 mm × 250 mm, 3 μm) with a mobile phase composed of 0.1% trifluoroacetic acid and acetonitrile in the ratio of 50:50 (v/v) which was run at a flow rate of 0.7 ml/min and the column temperature at 35 °C, detected by ELSD at a temperature of 55 °C. The retention time of sucralfate was 2.7±0.5 min. Linearity was acquired in the range of 500–2300 μg/ml. Results. The method was validated for accuracy, precision, repeatability, and robustness. HPLC chromatogram of sucralfate standard reference solution is attached. Assay of sucralfate tablets(Carafate, Australia) was carried out with 96.02 ± 6.33% of the labeled dose observed. Discussion. The proposed method is accurate, precise, and reproducible for the quantitative determination of sucralfate and was easy to apply to the assay of commercially available sucralfate tablets.

1. SP42-NF37 2S (2019).
4. ICH Guideline (2005), Validation of analytical procedures Q2 (R1)

Determination of residual N, N-dimethylformamide in drug eluting pharmaceutical formulations
Souha H Youssef1, Mohammad Arafat3, Sanjay Garg1. Clinical & Health Sciences, University of South Australia1, Adelaide, SA, Australia.

Introduction. The global pharmaceutical market for N,N-Dimethylformamide (DMF) currently exceeds $90 million and expected to increase by more than 14% in the next 7 years. Its high dissolving powers has made it the solvent of choice in many pharmaceutical processes including synthesis, purification and crystallization. However, DMF is a class 2 residual solvent which is considered potentially hepatotoxic. Its concentration in final pharmaceutical products are restricted by regulatory bodies to 880 ppm and a permissible daily exposure of 8.8 mg/day. Although gas chromatography (GC) is a common practice for determination of residual solvents, GC method described in USP does not detect the limit concentrations of DMF. Aims. Development of a simple, sensitive and selective HPLC method for the determination of residual DMF in anti-cancer drug eluting stents.

Methods. The mobile phase was composed of 50 mM NaH2PO4: Acetonitrile (95:5, v/v) and pH was adjusted to 6.5 using NaOH. A flow rate of 1 mL/min was applied, and detection carried out at 230 nm. Elution was performed with C8 column.

Results. The developed method demonstrated linearity at a range of 5-1000 ppm with an accuracy of 98.82 ± 1.79%(r²=0.9997). Limit of detection and limit of quantitation were determined as 2 and 4 ppm, respectively.

Discussion. The developed method offers a wider linearity range compared to reported methods and a short run time (Rt=5.3 min). This method has been applied for the determination of residual DMF in anti-cancer drug eluting stents, consequently, selectivity was evaluated in the presence of solvents and release media used in formulation processes such as phosphate-buffered saline, tetrahydrofuran, methanol, isopropyl alcohol and dimethylacetamide. The obtained results were within acceptable limits indicating the potential of the method to be applied for other pharmaceutical formulations.
Pharmacoepidemiology of metaraminol in critically ill patients with shock
Arwa A Sardaneh, Jonathan Penn, Matthew Oliver, David Gattas, Andrew J McLachlan, Asad E Patanwala.
School of Pharmacy, Univ of Sydney, Sydney, NSW; Royal Prince Alfred Hospital, Sydney, NSW.

Introduction. The lack of evidence on metaraminol use for the treatment of shock in evidence-based consensus guidelines has not limited its use in critical care. Data from multicentre randomised controlled trials and prospective observational studies have shown metaraminol is utilised in up to 42% of patients in shock.

Aims. To describe the pharmacoepidemiology of metaraminol use in critically ill patients with shock.

Methods. A retrospective observational study was conducted in a 54-bed intensive care unit in Australia. Patients admitted between October 2018 and October 2019 who received metaraminol infusions for the management of shock were included.

Results. A total of 152 patients were included. When metaraminol was used, it was the most common first-line vasopressor started for the management of shock (97%, n=147) and was used as monotherapy in 53% (n=81) of patients. The median duration of metaraminol infusion was 7 h (IQR 3 to 19) and the maximum metaraminol infusion rate used was 4.0 mg/h (IQR 2.5 to 6.0). Peripheral vasopressor infusions were utilised in 96% (n=146/152) of patients. In all of these cases, the peripheral vasopressor used was metaraminol (100%, n = 143/143). Patients were switched from metaraminol to noradrenaline infusions after the insertion of a central venous catheter (R²=0.89). Patients treated with metaraminol monotherapy (MET-M) had a lower APACHE III score (58 vs 68; p<0.01), a longer duration of metaraminol infusion (12 versus 5 h; p < 0.01), and a shorter duration of overall vasopressor use (12 vs 39 h; p <0.01), compared to those treated with combination vasopressors (MET-C).

Discussion. Metaraminol is often administered as a first-line peripheral vasopressor and is used as a single agent in patients with a lower severity of shock. Metaraminol is commonly transitioned to noradrenaline after the insertion of a CVC.

Tools to evaluate medication management for caregivers of people with dementia: a systematic review
Melissa Gench, Mouna J Sawan, Aili Langford & Danijela Gnjidic.
School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia

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

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

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

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

Discussion. Current tools capture specific aspects of medication management, with medication administration the most evaluated aspect of medication management. Future research is needed to develop a tool to holistically evaluate the complexities of medication management for caregivers of people living with dementia to minimise adverse events and reduce caregiver burden.
482

Vasopressor dose equivalence: a scoping review and suggested formula.

Shruti Goradia1, Anwa Abu Sardaneh1, Sujita W. Narayan1, Jonathan Penm1, Asad E. Patanwala1,2. Sydney Pharmacy School, The Univ of Sydney1, Sydney, NSW, Australia; Royal Prince Alfred Hosp2, Camperdown, NSW, Australia.

Introduction. The calculation of equipotent doses between vasopressor agents is necessary in clinical practice and research pertaining to the management of shock. This is done via calculation of norepinephrine equivalent (NE) doses based on conversion ratios between vasopressor agents. Currently, there are no evidence-based reviews supporting the conversion ratios used in NE calculations.

Aims. To summarise the conversion ratios between vasopressors that have been derived from the literature and provide a formula for researchers to incorporate into their study designs.

Methods. The databases Medline, Embase and Web of Science were searched from inception to 25th June 2020. Additional papers were obtained through a bibliography search of the retrieved articles. Two investigators independently assessed articles for eligibility. Clinical trials published in the English language in adult patients that compared the potency of at least two intravenous vasopressors (norepinephrine, epinephrine, dopamine, phenylephrine, vasopressin or metaraminol), with regard to an outcome of blood pressure, were selected. Conversion ratios were then grouped according to the vasopressor agent and the study setting and were reported in reference to one unit of norepinephrine. The final ratios were calculated as a weighted mean of the ratios from individual studies.

Results. The database and bibliography searches retrieved 14,762 articles. Of these, 19 articles were included for synthesis. The range of conversion ratios equivalent to one unit of norepinephrine were: epinephrine (0.7-1.4), dopamine (75.2-144.4), metaraminol (8.3), phenylephrine (1.1-16.3), and vasopressin (0.3-0.4). The following formula may be considered for the calculation of NE (all in mcg/kg/min, except vasopressin in units/min): NE = norepinephrine + epinephrine + phenylephrine/10 + dopamine/100 + metaraminol/8 + vasopressin*2.5.

Discussion. Our scoping review provides an evidence-based summary of equipotent ratios for the most common vasopressors used in clinical practice. The formula provided may be considered to calculate NE for future studies in the intensive care unit.

483

The prevalence of opioid analgesic use in people with chronic non-cancer pain: systematic review and meta-analysis.

Graeme Wertheimer1, Stephanie Mathieson2,3, Christopher Maher2,3, Christine Lin2,3, Andrew McLachlan4, Rachelle Buchbinder5,6, Sallie-Anne Pearson7, Martin Underwood8,9. School of Medicine, University of Notre Dame1, Sydney, NSW, Australia; Institute for Musculoskeletal Health2, Sydney, NSW, Australia; Sydney School of Public Health, Univ of Sydney3, Camperdown, NSW, Australia; Sydney Pharmacy School, Univ of Sydney4, Camperdown, NSW, Australia; Monash Dept of Clin Epi, Cabrini Institute5, VIC, Australia; Dept of Epidemiology and Preventive Medicine, Monash University6, VIC, Australia; Medicines Policy Research Unit, Centre for Big Data Research in Health, Univ of NSW7, Sydney, NSW, Australia; Warwick Clinical Trials Unit, Univ of Warwick8, Coventry, United Kingdom; Univ Hosp Coventry and Warwickshire9, Coventry, United Kingdom.

Introduction. The prevalence of opioid use in people with chronic non-cancer pain is unclear.

Aims. To review studies examining the proportion of people with chronic non-cancer pain who report consuming opioids and characteristics associated with their use.

Methods. We searched databases from inception to 8th February 2020. We included observational studies reporting the proportion of adults with chronic non-cancer pain who used opioid analgesics. Opioids were categorised as weak (e.g. codeine) or strong (e.g. oxycodone). Study risk of bias was assessed, and Grading of Recommendations Assessment, Development and Evaluation provided the overall quality. Results were pooled using a random-effects model. Meta-regression determined factors associated with opioid use.

Results. Sixty studies (N=3,961,739) reported data on opioid use in people with chronic pain from 1990-2017. Forty-six (77%) had moderate risk of bias. Opioid use was reported by 26.8% (95%CI 23.1%-30.8%; moderate quality evidence) of people with chronic pain. The use of weak opioids (17.3% (95%CI 11.9%-24.4%; moderate quality evidence) was more common than strong opioids (9.8% (95%CI 6.8%-14.0%; low quality evidence). Meta-regression determined opioid use was associated with geographic region (P=0.02; lower in Europe than North America), but not sampling year (P=0.77), setting (P=0.06), diagnosis (P=0.34) or disclosure of funding (P=0.77).

Discussion. Our review summarised data from over 3.9 million people with chronic non-cancer pain reporting their opioid use. Between 1990 to 2017, one quarter of people with chronic non-cancer pain reported taking opioids and this proportion did not change over.
Duration of postoperative opioid use after hip or knee surgery: a systematic review and meta-analysis

Hui Ping Tay1, Xinyi Wang1, Sujita W Narayan1, Jonathan Penn1, Asad E Patanwala1,2. School of Pharmacy, Faculty of Medicine and Health, the University of Sydney1, Sydney, NSW, Australia; Royal Prince Alfred Hospital2, Camperdown, NSW, Australia.

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

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

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

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

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

Effect of CYP2B6 516G>T on Plasma Efavirenz and 8OH-Efavirenz Concentrations in Papua New Guinea HIV patients

Helena Van Schalkwyk1, Natalia Bordin Andriguetti1, Joseph Tucci2, Paul Pumuye3, Daniel Barratt1, Andrew A Somogyi1. Disc Pharmacol, Univ Adelaide1, Adelaide, SA; Dept of Pharmacy & Applied Science, La Trobe Univ2, Bendigo, Vic; School of Medicine and Health Sciences, Univ Papua New Guinea3, Boroko, Papua New Guinea.

Introduction. Papua New Guinea (PNG) has the highest prevalence of HIV/AIDS in the Pacific with efavirenz (EFV) as the main treatment. EFV is mainly metabolised by CYP2B6 to 8-hydroxy-efavirenz (8OH-EFV). Very little is known about PNG EFV CYP2B6 genetics and its relationship to plasma efavirenz and 8OH-EFV concentrations and of the metabolic ratio of 8OH-EFV to EFV.

Aims. To determine the frequency of CYP2B6 516G>T in PNG HIV/AIDS patients receiving efavirenz treatment and to examine the relationship of 516G>T on plasma EFV, 8OH-EFV and the metabolic ratio.

Methods. Whole blood and plasma were collected from 154 PNG HIV/AIDS patients. EFV and 8OH-EFV plasma concentrations were determined by LCMS/MS. DNA was genotyped by MassArray panel through AGRF. Allele frequencies were compared to plasma EFV, 8OH-EFV and 8OH-EFV/EFV metabolic ratio. Further comparison was made between the genotypes and EFV therapeutic range (1-4 μg/mL).

Results. The T allele frequency was 53%. Of the patients that were homozygous variant (TT) for 516G>T, 66% were above EFV therapeutic range and only 17% fell within therapeutic range. Metabolic ratio’s range from 0.01 to 1.25 with an mean of 0.19. Discussion. PNG HIV/AIDS patients exhibit very high frequencies of CYP2B6 516G>T variant genotype, TT. This genotype has shown to have an influence whether a patient falls within EFV therapeutic range in this population. These genetics may have important implications for CYP2B6 substrate drugs in this population.
Current pharmacological and non-pharmacological interventions for illicit drug-induced presentations in emergency departments: A literature review

Ruby Tszwai Au1, Elizabeth Hotham1, Vijayaprakash Suppiah1,2. 1UniSA Clinical and Health Sciences, University of South Australia, South Australia, Australia; 2Australian Centre for Precision Health, University of South Australia, South Australia, Australia.

Introduction. High prevalence of illicit drug use in Australia is a concerning issue. Patients repeatedly presenting to emergency departments (EDs) due to illicit drug-induced psychosis may contribute to overburdening of EDs.

Aims. To investigate the current pharmacological and non-pharmacological interventions provided in EDs.

Methods. Literature searches were conducted in the following databases: Ovid MEDLINE, PubMed, Embase Classic + Embase, Ovid Emcare and APA PsycInfo. Only English language manuscripts published between 2015 to 2020 were included. 58 manuscripts were identified, and 18 were included in this literature review.

Results. Cannabis and meth/amphetamine were common illicit drugs consumed by patients presenting at EDs with clinical presentations, such as agitation, aggression, and acute psychosis. Lorazepam, haloperidol and olanzapine were the most prescribed pharmacotherapies. Other medications included antidepressants, mood stabilisers, anticonvulsants, vasopressors, sodium bicarbonate, ketamine, propofol, antihistamines and antidotes, such as naloxone. Physical and mechanical restraints were the most common non-pharmacological interventions, followed by intravenous fluid replacement, intubation and ventilatory support, seclusion, bedside consultation, counselling, psychoeducation, cognitive behavioural therapy, and cognitive remediation therapy. However, some patients with self-limited symptoms were not given any medical treatment, despite demanding clinician attention.

Discussion. The pharmacotherapies reported in recent studies were in line with guidelines. While verbal de-escalation was the recommended first line treatment, it was not reported in any studies reviewed. Additionally, the use of restrictive interventions in these studies may be inappropriate. Patients with self-limited symptoms unnecessarily consumed ED resources contributing to ED overcrowding. Overcrowding and extended waiting time in EDs were identified as factors that precipitate violent and aggressive behaviours, posing significant risks to the safety of ED staff. Individuals with illicit drug-induced presentations were also more likely to re-present to EDs, even on multiple occasions, highlighting the significant burden illicit drug use places on ED resources.

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

Mohammed B Ayalew1,2, Gudrun Dieberg3, Frances Quirk1, Joy M. Spark1. Faculty of Medicine and Health, University of New England4, Armidale, NSW, Australia; Department of Clinical Pharmacy, University of Gondar4, Gondar, Amhara, Ethiopia; Biomedical Science, University of New England4, Armidale, NSW, Australia.

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

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

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

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

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

Tien Ngoc Thi Bui1, Elizabeth Hotham3, Mark Loughhead1,2, Nicolas Procter1,2, Sara McMillan3, Fiona Kelly3 Vijayaprakash Suppiah1,4, 1UniSA Clinical and Health Sciences, University of South Australia, Adelaide, Australia. 2Mental Health and Suicide Prevention Research Group, University of South Australia, Adelaide, Australia. 3Quality Use of Medicines Network, Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia. 4Australian Centre for Precision Health, University of South Australia, Adelaide, Australia.

Introduction. It is vital that patients have an adequate level of understanding and knowledge of their medications for treatment success. However, medication education provided by healthcare providers may be inadequate. This is particularly concerning, especially for people living with mental health conditions as it has been previously reported that they receive less information from doctors and pharmacists than people with other medical conditions.

Aim. To explore the knowledge and attitudes of clients living with mental health conditions towards their medications and to study their experiences with healthcare providers.

Methods. Focus group sessions were conducted at a community-managed specialist mental health service provider with clients living with mental health conditions.

Results. Thirteen participants and two peer support workers participated in two focus group sessions. Responses indicated that participants did not feel confident in their knowledge of their prescribed medications as most participants did not seem prepared for the adverse drug reactions. This was commonly attributed to inadequate medication education, with a limited number reporting effective interaction with pharmacists. The majority of the participants also reported that they did not receive any form of written information and often resorted to seeking information on the internet. In addition, the participants expressed the need for a client-centred holistic care approach, involving direct communication between all healthcare providers.

Discussion. Findings indicated that there is a gap in medication education provided to clients living with mental health conditions, with the amount and quality of medication education given varying considerably. There is a need for immediate action to address this gap. Future research should consider exploring the scope for further medication education in the community setting such as at non-for-profit organisations.

Medication safety during ICU care transfers with an Electronic Medication Management System

Racha Dabliz1, Simon K. Poon2, Greg Fairbrother4, Angus Ritchie3,4, Garry Soo5, Rosemary Burke6, Mark Kol1,7, Rebecca Ho6, Linh Thai5, Jacqueline Laurens4, Sergei Ledesma4, Arwa Abusardaneh5 Tracy Leung6 Ana L. Hincapie9 Jonathan Penm1

1. The University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, NSW, Australia
2. School of Computer Science, University of Sydney, Sydney, NSW, Australia
3. Concord Clinical School, University of Sydney, Sydney, NSW, Australia
4. Health Informatics Unit, Sydney Local Health District, Concord, NSW, Australia
5. Pharmacy Department, Concord Repatriation General Hospital, Sydney, NSW, Australia
6. Pharmacy Services, Sydney Local Health District, NSW, Australia
7. Intensive Care Services, Concord Repatriation General Hospital, Sydney, NSW, Australia
8. Pharmacy Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia
9. Ana L. Hincapie, Winkle College of Pharmacy, University of Cincinnati, OH, USA

Introduction. For patients requiring admission to the Intensive Care Unit (ICU), transfers of care (TOC) during admission/discharge from the ICU are high-risk periods for medication errors. Within Australia, commonly general wards and the ICU do not share an integrated Electronic Medical Record and specifically an Electronic Medication Management System (EMMS) as part of the EMR.

Aims. To evaluate the effect of a hospital wide integrated EMMS on medication error rates during ICU TOC.

Methods. A 6-month historical control study was performed before and after implementation of the EMMS in the ICU of a tertiary hospital. Prescribing errors detected by pharmacists in the study period were divided into phase 1, (pre-EMMS, 6months), phase 2 (3 months post implementation after shakedown stage) and phase 3 (next 3 months of post implementation). They were categorized as prescribing error types under system or clinical intervention. Chi square statistics and interrupted time series analysis were used to assess the change in the proportion of patients who had an error at TOC during each phase. Logistics regression was used to determine the relationship between error type and study phase.

Results. TOC errors occurred in 42%, 64% and 19% of patients in phase 1, 2 and 3 respectively. There was a significant decline in the proportion of patients with an error between phase 1 and 3 (p<0.01). During phase 1, the proportion of patients with an error were increasing by 4.6 patients per month over the 6-months. Error rates reduced by 95% (95%CI= -103.5 to −46.7, P<0.01) by the end of phase 3. Of the error types, two system error categories ‘wrong rate/frequency’ and ‘drug omission’ showed a significant decrease between phase 1 and 3. All other error categories showed no significant change.

Discussion: Medication errors during TOC reduced following implementation of an integrated ICU EMMS. Added safeguards in hospitals such as, pharmacist interventions following implementation of an EMMS could reduce the risk of medication errors.
Exploring Pharmacy Ethics in developing countries – a scoping review

Leen B. Fino1,2, Iman A. Basheti1,2, Bandana Saini1, Rebekah Moles1, Betty B. Chaar1. The University of Sydney1, School of Pharmacy, Faculty of Health and Medicine, Sydney, NSW, Australia; Applied Science University2, Faculty of Pharmacy, Amman, Jordan

Introduction. Healthcare ethics have been profoundly influenced by principles of bioethics that emerged post-World War II in the Declaration of Geneva 1948. ‘Beneficence’, ‘Non-Maleficence’, ‘Justice’ and ‘Respect for Autonomy’, have become foundational principles of contemporary medical codes of ethics. These principles are well reflected in most professional pharmacy code of ethics globally. This domain remains relatively unexplored in most developing countries and the majority of what has been published in this area relates to Western cultures. There have been no attempts to pool findings from a similar scope of research emanating in developing countries.

Aim. This study aimed to explore the scope of pharmacy ethics in the literature pertaining to developing countries.

Methods. An extensive search of three relevant databases was conducted from Jan 2000 to July 2019, in order to identify relevant studies conducted in or focussed on ethics in pharmacy in developing countries.

Results. The full text of 20 relevant articles that met inclusion criteria were critically analysed and qualitatively categorised into three emerging themes; Ethical challenges in pharmacy practice, Approaches used in teaching pharmacy ethics, and Code of ethics analysis and implementation.

Discussion. Findings of this literature review illuminated a gap in pharmacy ethics literacy in developing countries and in pharmacists’ ethical attitudes in handling ethical dilemmas, as well as a lack of familiarity with contemporary ethical principles and codes of ethics. In most developing countries pharmacists’ lack of respect for patients’ autonomy and pharmacists being prone to financial pressure were found to have a significant impact on pharmacy practice.

Pharmacist’s and physiotherapist’s perspectives about sports pharmacy

Alison D Hooper1, Joyce M Cooper1, Jodie Marquez2, Therese Kairuz1. School of Biomedical Sciences & Pharmacy, Faculty of Health & Medicine, University of Newcastle1, Callaghan, NSW, Australia; School of Physiotherapy, Faculty of Health & Medicine, University of Newcastle2, Callaghan, NSW, Australia.

Introduction. Sports pharmacy is an emerging field. Although sports-related injuries in primary care are often managed by physiotherapists, consumers can seek advice and purchase medicines and products from community pharmacists. However, the scope of practice of pharmacists in sports medicine has not been reported.

Aims. This qualitative study aims to explore perceptions of pharmacists and physiotherapists about current and potential roles in sports pharmacy, to provide insight into barriers to, and facilitators of, pharmacist input.

Methods. A total sample (n=32) of equal numbers of pharmacists and physiotherapists was proposed. Using a snowballing technique, AHPRA-registered pharmacists and physiotherapists were invited to participate in semi-structured interviews conducted from August 2020 (ongoing). Interviews were transcribed for qualitative coding and thematic analysis. Due to COVID-19, interviews were conducted via Zoom.

Results. Preliminary analyses from 11 interviews indicate that pharmacists currently have varied roles in what they perceive as being sports-related health care. Pharmacists are frequently called upon to provide sports-related health advice and are enthusiastic about their involvement. However, apparent barriers include lack of knowledge and training opportunities. Physiotherapists perceive the current role of pharmacists as being limited to the provision of medicines and medicines advice, and are willing to refer patients to a pharmacist for advice about the safe use of medicines. Physiotherapists are positive about collaborating with pharmacists in providing sports-related health care.

Discussion. Interviews and data collection are ongoing. Nevertheless, preliminary findings indicate that pharmacists are currently providing advice about a range of sports-related topics. Pharmacists feel most confident when providing advice about medicines, including prohibited substances, and triaging patients, but lack confidence in their knowledge about musculoskeletal injury and healing, supplements, strapping tape and devices/supports, despite receiving frequent requests for advice. Physiotherapists are positive about pharmacists’ roles in sports health, but are uncertain about pharmacists’ scope and expertise. Training opportunities and resources will be needed to support pharmacists in these roles, and future research should explore consumer perspectives about sports pharmacy.
492

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

Karlee Johnston1. Medical School, Australian National University2, Canberra, ACT, Australia

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

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

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

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

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


493

Deprescribing opioid analgesics: An overview of systematic reviews

Aili Langford1; Carl R Schneider1; Jack C Collins1; Benita Suckling1; Chung-Wei Christine Lin2; Lisa Bero3; Danijela Gnjidic1. School of Pharmacy1, USYD, Sydney, NSW; Institute for Musculoskeletal Health2, USYD, Sydney, NSW; School of Medicine3, University of Colorado, Colorado, USA.

Introduction. Clinical practice guidelines suggest that opioid analgesics should only be prescribed when necessary, in the lowest effective dose, and for the shortest duration. Reduction of prescribed opioids can be challenging and interventions to assist deprescribing may be of value to health care professionals and opioid consumers.

Aims. To synthesise and evaluate published evidence from systematic reviews examining the effectiveness of interventions to support opioid deprescribing.

Methods. Comprehensive searches in CINAHL, Cochrane Library, EMBASE and MEDLINE were undertaken to identify systematic reviews which examined interventions for prescribed opioid reduction or cessation. Eligible articles were peer-reviewed systematic reviews, published in the English language from March 2010 to March 2020. The primary outcome was reductions in opioids, measured in morphine milligram equivalents. Secondary outcomes were assessed where reported and included pain scores, quality of life measures, adverse events, and physical and psychological function. Two reviewers independently extracted information and scored methodological quality using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) tool. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was applied to assess the evidence quality, with evidence summarized and conclusions compared across reviews via narrative synthesis.

Results. Eighteen reviews were found eligible for inclusion. Pharmacological (n=3), physiological (n=10), psychological or behavioural (n=4) and health system interventions (n=4) were examined. Rates of opioid reduction and discontinuation varied widely across reviews and interventions. Pharmacological and psychological based interventions showed the greatest reductions in MME within the study periods. Similarly, evidence suggests some improvements in patient outcomes such as pain severity, physical and psychological function and quality of life when opioids are deprescribed.

Discussion. Several types of interventions may be effective in supporting opioid deprescribing. Positive clinical outcomes for pain severity and quality of life may result from efforts to deprescribe opioids.
Extended roles in Aotearoa New Zealand community pharmacy: The views of service users

Caroline Morris1, Janet McDonald2, Tara Officer2, Ausaga Fa‘asalele Tanuvasa2, Nora Parore2, Kirsten Smiler2, Jacqueline Cumming3, Dept Primary Health Care and General Practice, University of Otago1, Wellington, NZ; Health Services Research Centre, Victoria University of Wellington1, Wellington, NZ

Introduction. Internationally, pharmacy models of care, services and funding are developing to ensure better use of the skills of the pharmacist workforce. This trend is reflected in Aotearoa New Zealand (ANZ) with extended roles for community pharmacists (CPs) developing in relation to both individual patient care and population health. Role expansion has the potential to facilitate improvements in health outcomes and reduce inequalities.

Aims. To understand current developments in community pharmacy services in ANZ including the extent to which the expansion of roles is successfully occurring and what the enablers or barriers to progress might be.

Methods. Twenty-one semi-structured, audio-recorded interviews were conducted face-to-face or by telephone, with users of extended community pharmacy services. Participants were recruited in 2019/20 from 8 diverse case study sites. Interviews were transcribed verbatim, coded and analysed thematically.

Results. Preliminary analysis has identified that service users have mixed recognition of the different roles of staff within the pharmacy, with the role of pharmacy technicians poorly understood. A range of factors potentially influenced the uptake of extended services offered by the pharmacy including trust in the staff and a respectful and comfortable relationship, together with confidence in the CPs’ knowledge and skills, along with ease of access to the pharmacy and convenience. Lack of awareness of the scope of extended services on offer was a potential barrier to uptake. Despite this, a positive experience with one specific service sometimes promoted an explicit acceptance of other roles and extended services. While the financial cost of a service was not necessarily a barrier for an individual interviewee, many acknowledged that it may be for others.

Discussion. A trusting and respectful relationship between pharmacy staff and service users, and optimal promotion of the extended services on offer are key facilitators to uptake. These case studies (also including interviews with a variety of pharmacy staff and local healthcare professionals) are the final stage of a larger study exploring the contexts in which changes in community pharmacy services in ANZ are occurring, the health and health service outcomes that are expected to result and the mechanisms producing change.

Interventions at hospital discharge to guide caregivers in medication management for people living with dementia: A systematic review

Mouna Sawan1, Damian Wennekers2, Marissa Sakiris1, Danijela Gnjidic1,2, Syd Pharm School, Faculty of Med and Health2, Univ of Sydney, NSW, Australia; School of Medicine; School of Pharmacy, Faculty of Science3, University of Utrecht, Utrecht, The Netherlands; Charles Perkins Centre2, The University of Sydney, Camperdown, NSW, Australia

Introduction. Hospital discharge has a significant impact on the continuity of care for people living with dementia. Clear guidance on medication management should be provided to caregivers of people living with dementia to ensure appropriate use of medications post-discharge.

Aims. Identify and appraise the impact of interventions at hospital discharge to guide caregivers in the medication management for people living with dementia.

Methods. A systematic search of original studies was performed in Medline, Embase, PsycINFO and CINAHL. Articles published in English that reported on interventions to guide caregivers in medication management for people living with dementia were included. Two authors independently reviewed titles and abstracts.

Results. A total of five studies were included with a range of interventions that were typically delivered post-discharge by a multidisciplinary team and most targeted administration of medications by caregivers. Overall, three types of discharge interventions were identified including a pre-discharge caregiver educational intervention, a post-discharge caregiver support intervention, and medical discharge intervention at transitions of care. Of these, a pre-discharge caregiver education demonstrated shorter hospital stay (25 days vs 31 days, p=0.005). A post-discharge intervention that included follow-up visits reported lower use of high-risk medications (19% vs. 40%), and reduction in 30-day re-hospitalisation rates (11% vs 20%). In contrast, in another post-discharge intervention study, no difference in one-month re-hospitalisation rates (8.4% v 8.0%, p=0.818) was demonstrated. In another study, a post-discharge hospital educational program provided to caregivers found caregiver burden significantly decreased from 31.7 ± 17.6 (SD) pre-intervention to 27.7 ± 16.9 (SD) post-intervention (p=0.037).

Discussion. Current findings suggest there is a need for holistic interventions to guide caregivers in all aspects of medication management for people living with dementia, and should include support for caregivers in care coordination.
496

Role of medication beliefs on medication adherence in hypertensive Middle Eastern refugees and migrants in Australia

Wejdan Shahin.1 Ieva Stupans.1 Gerard Kennedy.2 Health and biomedical Science, RMIT University, Melbourne, VIC, Australia1. School of Science, Psychology & Sport, Federation University, Ballarat, VIC, Australia. 2

Introduction. Adherence to medications continues to rank as a major clinical problem in the management of patients with essential hypertension. Patients’ behaviour of taking medications may be influenced by their beliefs about medications. Different populations such as refugees, and migrants may have different perceptions about their prescribed medications, which may influence their medication adherence.

Aims. To evaluate the impact of medication beliefs on medication adherence, and to assess the potential differences between refugees and migrants, in medication adherence and medications beliefs.

Methods. A cross-sectional study (n= 319 Middle Eastern refugees and migrants) was conducted using a survey that links Beliefs about Medicine Questionnaire (BMQ) and the Medication Adherence Questionnaire. BMQ scores (necessity and concerns scales) were classified as “accepting”, “indifferent”, “ambivalent” or “skeptical”.

Results. There were significant associations between medication adherence and necessity and concerns scales. Refugees were likely to have less necessity, and more concern beliefs than migrants. They were also less likely to adhere to medications. Refugees and migrants with “accepting” beliefs reported the highest adherence to medication and those holding “skeptical” beliefs reported the lowest adherence.

Discussion. Following from the findings of this study, interventions to improve medication adherence need to focus on the ‘skeptical’ and ‘ambivalent’ clusters. Understanding the characteristics of each of these clusters by healthcare providers may lead to appropriate interventions for improving medication taking behaviours.

497

A pilot pharmacist health coaching trial investigating changes to modifiable health behaviours

Harjit K Singh1, Gerard A Kennedy2,1, Ieva Stupans1. The School of Health and Biomedical Sciences, RMIT University1, Melbourne, VIC, Australia. School of Science, Psychology and Sport, Federation University2, Ballarat, VIC, Australia.

Introduction. Pharmacists have used health coaching to improve patient management of hypertension in a number of international settings, but the provision of the service by Australian community pharmacists has been limited. During health coaching, the stages of change (SOC) approach can be applied to motivate and facilitate progress towards positive health behaviour change. This approach has been previously used by Australian pharmacists but has been confined to smoking cessation services. The application of the SOC model by pharmacists has involved interviews and questionnaires, which although convenient do not provide a realistic representation of the cyclic nature of the SOC. Thus, we have used a dynamic measure of SOC to evaluate the outcomes of health coaching by Australian community pharmacists in patients with poorly controlled hypertension.

Aims. To investigate whether pharmacist health coaching improves progression through the SOC for three-modifiable health behaviours: diet, exercise, and medication management in participants with poorly controlled hypertension.

Methods. Stages of change charts were developed for three-modifiable behaviours. In this pilot clinical controlled trial community pharmacist’s health coached 20 participants with poorly controlled hypertension at monthly intervals. Changes in systolic hypertension and SOC with respect to the three modifiable health behaviours were assessed at session 1 and 4. To substantiate the behaviour change outcomes, SOC were also assessed in a validation group.

Results. Statistically significant changes in the modifiable health behaviours- medication management (p = 0.03) and exercise (p = 0.01) were apparent in participants who received health coaching and were evident through positive changes in the SOC charts. This correlated with a decrease in mean systolic blood pressure from session 1 to session 4 by 7.53mmHg (p<0.05). The participants in the validation group did not experience significant changes with respect to the SOC.

Discussion. Pharmacists successfully utilised the dynamic SOC tool to assess patient’s readiness to change and facilitate progress in three modifiable health behaviours parallel to an improvement in systolic blood pressure. These results pave way for the application of the SOC tool by pharmacists to guide management of other chronic conditions.
Exploring contributing factors of acute psychological impact in community pharmacists due to COVID-19 pandemic.
Blake McCallum1, Kay Dunkley2, Elizabeth Hotham3, Vijayaprakash Suppiah1,3. 1UniSA Clinical and Health Sciences, University of South Australia, South Australia, Australia; 2The Pharmacists’ Support Service, Victoria, Australia; 3Australian Centre for Precision Health, University of South Australia, South Australia, Australia.

Introduction. The world continues to suffer through the coronavirus pandemic. Community pharmacists working throughout the pandemic faced an ‘onslaught’ of frustration and confusion from the public whilst desperately trying to maintain access to required medicines for all Australians. The Pharmacists’ Support Service (PSS) run by pharmacists for pharmacists, interns, and pharmacy students across Australia provides a call-in service.

Aim. To identify contributing factors of acute psychological impact from issues raised by pharmacists in their calls to the PSS during the pandemic.

Methods. De-identified data from all calls received by the PSS during the study period (February to May 2020) were categorised as those specifically mentioning COVID-19 and those that did not. Data from calls in the same period in 2019 served as a comparator. Categorical data were analysed using a two-tailed chi-squared test. Thematic analysis of the qualitative data was conducted.

Results. The PSS noted a 31% increase in calls during the peak of the pandemic when compared to the same period last year. Most callers were community pharmacists (average 91%) with 79% of all calls related to emotional or psychological issues, including stress, anxiety and concerns about their own mental health. Workplace conflicts and concerns over workload were other issues raised by pharmacists.

Discussion. A significant proportion of callers had discussed anxiety and stress, workplace conflict, perceived bullying, extreme workloads, and job dissatisfaction, highlighting the highly stressful work of community pharmacists during this pandemic. Existing literature from Australia and around the world has highlighted concerns about these increasing pressures and the impact on pharmacists and their ability to appropriately provide safe access to, and advice about medicines. To fully understand the long-term psychological impact of the current pandemic, a larger study following a cohort of community pharmacists longitudinally over the next few years is required.

A qualitative study exploring barriers to and facilitators of medication adherence in Ethiopia: hospital pharmacists’ perspectives
Henok G. Tegegn1,2, Stuart Wark1, Edouard Tursan D’Espaignet1, M. Joy Spark1. School of Rural Medicine, University of New England1, Armidale, NSW, Australia; Clinical Pharmacy, University of Gondar2, Gondar, Amhara, Ethiopia.

Introduction. Ethiopian pharmacists are involved in providing direct patient care services that assist patients with medication adherence. However, no studies have explored pharmacists’ perspective and experience of medication adherence.

Aims. To explore hospital pharmacists’ insights into barriers to and facilitators of medication adherence in Ethiopia.

Methods. Semi-structured face to face interviews with hospital pharmacists, actively involved in direct patient care, were conducted via Zoom/Skype. All interviews were audiotaped, transcribed verbatim, translated into English and analysed using thematic analysis to identify main themes and subthemes.

Results. A total of 14, mostly male (12), participants participated in the study. Five main themes emerged including an overview of medication adherence and its assessment, perceived roles of pharmacists in medication adherence, enablers of, and barriers to medication adherence and ways forward. The majority of pharmacists perceived that challenges in medication adherence start with its assessment. This was thought to be due partly to lack of daily assessment in healthcare, absence of cost-effective and validated tools, and low use of combined tools in Ethiopia. Other barriers identified were dosage form preference, disease conditions, treatment, health care system, and the government/national policies at large. Availability of a counselling room and drug information centre, patients’ interest and readiness for cooperation, subsidization and free drug programs, and supportive patient orientated pharmacy curriculum were some of the facilitators identified by pharmacists. Pharmacists suggested several ways forward specific to each identified barrier including prioritizing patients for available interventions and simplifying complex medication regimen and strengthening of the existing facilitators to improve medication adherence.

Discussion. The findings of this study could be integrated into intervention programs, policy and curriculum to improve medication adherence in daily clinical care, and research projects. Patients’ preference for dosage forms has not been reported previously and should be considered along with medication complexity and medication knowledge when considering medication adherence.
500

Implementation of a customised automation tool to optimise pharmacy practice
Will Tumusiime¹, Aaron Van Garderen². Pharmacy department, Ipswich Hospital¹, Ipswich, Qld, Australia; Pharmacy department, Logan Hospital², Logan, Qld, Australia;

Background. The implementation of the electronic Medical Record (eMR) has introduced many benefits to improving healthcare delivery. The literature cites conflicting reports with respect to the expected benefits in saving clinician time; increased documentation and negative user experience.

Description. Two Queensland Health Hospital pharmacy departments implemented a customised automation tool, into their pharmacy workflow. It is a free, open-source scripting language for Windows that allows users to easily create small or complex scripts. It allows the creation of keyboard shortcuts which can automate repetitive tasks such as launching specific internet sites. Core activities in the pharmacy work practice were identified as being aligned to this technological process; pharmacist medication annotations and electronic intervention forms.

Action. Using a prospective observational study design this project consisted of two parts; a four-week trial of the autotext tool, followed by a questionnaire to assess the perceived effectiveness. Prior to commencement of the trial, the autotext tool was built and customised to suit clinical pharmacist workflows. Education was tailored to staff at both sites on tool use.

Evaluation. In both hospitals over 70% of pharmacists either agreed or strongly agreed with all Likert statements which indicates that they believe the autotext tool will facilitate improved user experience, greater productivity, and improved workflow. The pharmacists at both sites found intervention documentation the most useful feature of the tool. At both sites over 90% of participants agreed that the autotext tool was easy to use. Education was identified as a key requirement.

Implications. The autotext tool is an effective method for improving workflow, reducing the time needed for documentation and increasing the time spent in clinical duties. The benefits of the tool were realised at both hospital sites.

501

The impact of QHMAC LAM restrictions on the prescription qty of oxycodone prescribed on discharge
Will Tumusiime¹. Pharmacy department, Ipswich Hospital¹, Ipswich, Qld, Australia;

Background. Australia wide opioid supply has increased significantly over the past three decades with oxycodone being the main contributor. Several studies have shown that the quantity of opioids supplied on initial prescription positively correlates with the probability of prolonged unnecessary use. To address this, in July 2019 the Queensland Health Medicines Advisory Committee (QHMAC) made a formulary change which restricted the quantity of immediate release oxycodone 5mg tablets prescribed on discharge to a maximum of 10-tablets.

Aim. To determine whether the QHMAC formulary restrictions led to a reduction in the quantity of oxycodone tablets prescribed on discharge in a 300-bed outer metropolitan hospital.

Method. Data from the electronic prescribing software Cerner was downloaded for a 12-month period from March-2019 to February-2020 which captured 6 months of prescribing data pre and post the QHMAC intervention. The proportion of 20-tablet prescriptions was compared with the quantity of 5 or 10-tablet prescriptions.

Results. A Chi-squared analysis found a significant reduction in the proportion of 20-tablet prescriptions which coincided with an increase in the proportion of 5/10-tablet prescriptions in both the surgical (p=<0.001) and medical (p=0.001) divisions of the hospital. This suggests that the formulary change led the doctors to prescribe lower quantities of opioids on discharge. No change in prescribing practice was identified in the emergency department. A number of contributors to this result were considered; lack of pharmacist presence; emergent nature of presentations; rebound presentations out of primary care hours; prescriber education and support.

Conclusion. The results demonstrate the effectiveness of QHMAC formulary restrictions in driving practice change and reducing opioid prescribing. It is acknowledged that there are multifaceted factors of opioid use and prescribing but this single step should not be overlooked as a part of raft of interventions that can be used.
An audit of the appropriateness of antipsychotic prescribing for cognitive impairment
Ruby Cole¹, Jessica Hawula¹, Will Tumusiime¹, Caitlin Hardman¹. Pharmacy department, Ipswich Hospital¹, Ipswich, Qld, Australia;

Introduction. The Aged Care Royal Commission highlighted the increasingly inappropriate use of antipsychotics for responsive behaviours associated with cognitive impairment. Despite limited published data on the extent that hospitals contribute to this problem, there are possible links between hospital prescribing and inappropriate continuation post-discharge.

Description. To assess the appropriateness of antipsychotic prescribing against industry guidelines in elderly patients over 65 years (over 45 for Aboriginal and Torres Strait Islander people) at a 300-bed regional Australian hospital.

Method. A retrospective audit of patients prescribed an antipsychotic between July and December 2019 was conducted to evaluate antipsychotic prescribing against the Australian Therapeutic Guidelines. Participants were excluded if they were receiving antipsychotic treatment for bipolar disorder, schizophrenia, post-operative nausea and vomiting or palliative care.

Results. The final cohort consisted of 141 participants, 36.9% being residential aged care facility (RACF) residents. First-line therapy including treatment of potential underlying causes of delirium and non-pharmacological interventions was documented in only 48.4% of patients. A new antipsychotic was prescribed in 75.9% of participants, 31.8% being RACF residents. Only 16.2% of all prescribed antipsychotic doses and frequencies aligned with industry guidelines, mostly due to regular dosing rather than recommended once-only or when-required dosing. While current guidelines advise review and immediate de-escalation of all antipsychotics upon symptom resolution, 48.2% of initiated antipsychotics were continued on discharge with just under 50% discharged to RACFs. Despite best practice guidelines recommending review of ongoing antipsychotic use, 47% of prescribed antipsychotics were unreviewed home medications and a mere 8.8% had documented plans for review post-discharge.

Discussion. This audit found antipsychotic prescribing had extremely poor adherence to industry guidelines, with an alarming number continued upon discharge without a documented plan for review. This potentially contributes to inappropriate antipsychotic use in RACF facilities and the wider community.

Virtual Renovation of the Medication and Pharmacist Engagement Clinic (MAPEC)
Will Tumusiime¹, Caitlin Hardman¹, Jess Sanders¹. Pharmacy department, Ipswich Hospital¹, Ipswich, Qld, Australia;

Background. In response to the Covid-19 pandemic, to ensure consistency with statewide directives of social distancing and where possible, to facilitate work from home models of care, the Medication and Pharmacist Engagement Clinic (MAPEC) at Ipswich Hospital underwent a virtual renovation.

Description. To continue the provision of a comprehensive medication counselling clinic, whilst minimizing face-to-face contact, MAPEC was overhauled to facilitate a virtual pharmacy clinic model. Instead of seeing patients in person, they were now seen via telehealth or phone calls by a pharmacist working from home.

Action. In addition to the use of standard remote desktop technology to access onsite programs such as ieMR and eLMS, two additional modes of technology were developed and incorporated to provide pharmacy care.

- The Queensland Health virtual clinic software – a program that facilitates face to face remote interaction via video calls. It was incorporated to enable personal and effective counselling.
- A customised data analytics application – developed in association with the IT department using the platform Qlik sense. The application is used to identify patients who had been discharged within the past 24 hours. In addition to pharmacist referrals, patients discharged out of pharmacy hours were identified and contacted, capturing a broader cohort than the prior model.

Evaluation. The virtual clinic model saw a 36% increase in the number of patients who were counselled from an average of 11 patients/day to 15 patients/day. The changes also enabled the pharmacists to contact patients discharged outside of business hours who would not usually receive a medication counselling service.

Implication. Developing and utilising technology in conjunction with a remote telehealth clinic can increase clinic capacity and enable follow up of patient cohorts who would ordinarily miss the pharmacy discharge service due to discharging out of hours. This can be achieved without a reduction in the quality of care provided.
504


Natalia Bordin Andriguetti1, Helena Van Schalkwyk1, Daniel Barratt1, Joseph Tucci1, Paul Pumuye3, Andrew A Somogyi1
Disc Pharmacol, Univ Adelaide1, Adelaide, SA. Bendigo Campus, La Trobe Univ2, VIC. Sch Medicine, Univ Papua New Guinea3, Port Moresby, Papua New Guinea.

Introduction. HIV/AIDS significantly impacts the health of the people of Papua New Guinea (PNG). Efavirenz (EFV) was prescribed as the preferred drug therapy for HIV/AIDS in PNG for two decades until recently, when it was replaced by dolutegravir. The unique genetics of PNG HIV/AIDS patients may place many of them at higher risk of major side effects related to high plasma EFV concentrations (Tucci et al., 2018). EFV is mainly metabolised to the inactive 8-OH-EFV.

Aims. Evaluation of EFV and major metabolite exposure through the quantification of plasma concentrations by LCMS/MS and side effects occurrence in PNG HIV/AIDS patients.

Methods. One hundred and fifty-five patients under therapy with EFV (600 mg/day) participated in the study after giving written informed consent. The plasma concentrations of EFV and 8-OH-EFV were determined by a LCMS8040 triple quadrupole MS using a C18 column for analytes’ separation after supported liquid extraction. CNS and psychiatric side effects were evaluated with yes/no to symptom questions reported by the patients.

Results. Patient’s age ranged from 14 to 65 years with body weights ranging from 36 to 120 kg. Mean±SD (range) concentrations for EFV and 8-OH-EFV were 2443±2303 (42 to 13211) and 271±205 (25 to 935) ng/mL, respectively. The mean 8-OH-EFV/EVF concentration ratio was 0.18±0.19 (0.01 to 1.25). Two patients had undetectable concentrations of EFV and 8-OH-EFV. Considering the EFV therapeutic range (1000-4000 ng/mL), 93 of the total patients (58%) had concentrations within, 36 (23%) below and 26 (16%) above the range. Eighty-five of 155 patients reported side effects, comprising 57 CNS, 8 psychiatric and 20 with both side effects. There was no apparent relation between plasm EFV or 8-OH-EFV and the occurrence of side effects.

Discussion. The results demonstrate extremely large interindividual variability in plasma EFV concentrations and metabolic ratios among PNG HIV/AIDS patients, likely due to CYP2B6 genetic polymorphism.


505

Cefepime-Induced Neurotoxicity: Identifying the Toxicity Threshold

Cindy Lau1,2, Deborah Marriott3,4, Michael Gould4, David Andresen3,5, Stephanie E Reuter4, Johannes Alffenaar3, Jonathan Penn2. Department of Pharmacy, St Vincent’s Hospital1, Sydney, NSW, Australia; The University of Sydney, School of Pharmacy, Faculty of Medicine and Health2, NSW, Australia; Department of Clinical Microbiology and Infectious Diseases, St Vincent’s Hospital3, Sydney NSW, Australia; School of Medicine, University of New South Wales4, Sydney, NSW, Australia; School of Medicine, University of Notre Dame5, NSW, Australia; School of Pharmacy and Medical Sciences, University of South Australia6, Adelaide, SA, Australia.

Introduction. Cefepime-induced neurotoxicity (CIN) has been demonstrated to be associated with cefepime plasma concentrations, however the toxicity threshold remains unclear.

Aims. The primary objective was to identify the cefepime plasma trough concentration at which neurotoxicity occurs. Secondary objectives were to determine the incidence of CIN at a tertiary institution, and to identify patient factors associated with the development of CIN.

Methods. A retrospective review of all patients administered cefepime between October 2017 and May 2018 in a tertiary hospital was conducted to determine total incidence of CIN. A Receiver-Operator Characteristic (ROC) curve was constructed to review the sensitivity and specificity of using various cefepime trough plasma concentrations to predict neurotoxicity. A regression was conducted to identify patient factors associated with CIN.

Results. In total, 206 patients were administered 259 courses of cefepime, with an overall incidence of CIN of 6% (16/259 courses). 64 courses had a cefepime trough concentration measured (24.7%). A cefepime trough concentration of 36 mg/L provided the best differentiation between patients who experienced neurotoxicity and those who did not. No other patient covariates were identified to be significantly associated with CIN.

Discussion. A cefepime trough plasma concentration > 36 mg/L was associated with CIN. The use of cefepime therapeutic drug monitoring may assist in the prevention of CIN by targeting trough concentrations < 36 mg/L. The retrospective design and small patient numbers were limitations of this study. A prospective study in a larger population is warranted given the wide disparity of results from existing studies investigating the toxicity threshold.
Green tea extract and its metabolites induce biochemical changes linked to hepatotoxicity in HepG2 cells

Garth L Maker¹, Emily Davies¹, Natasha Morrison¹. Medical, Molecular & Forensic Sciences, Murdoch University¹, Perth, WA, Australia.

Introduction. Green tea extract (GTE) is commonly used for its wide range of purported health benefits, but has been implicated in over 50 cases of liver damage in the last 20 years (Mazzanti, 2015). However, little is currently known in regards to which biochemical pathways are affected during GTE-induced hepatotoxicity.

Aims. This study aimed to determine the chemical composition of GTE and its metabolites, and to examine the biochemical pathways that are affected by exposure of HepG2 cells to these compounds.

Methods. Chemical composition of GTE products was investigated using GC-MS. GTE and individual catechins were metabolised with S9 human liver fraction and profiled using GC-MS metabolomics. HepG2 cells were exposed to GTE, catechins and their metabolites for 24 h and resulting biochemical changes determined using GC-MS metabolomics.

Results. Metabolism of GTE occurred with 17 metabolites produced, 10 of which were also produced by metabolism of catechins. Exposure of HepG2 cells to GTE significantly decreased amino acids, oxoacids and carboxylic acids at 1 mg/mL, but produced a different profile at 0.1 mg/mL. Exposure to metabolites of GTE caused changes in amino acids, carbohydrates and fatty acids in all treatment groups.

Discussion. This study suggested that GTE causes disruption to cellular lipids, proteins, nucleic acids and the mitochondria in HepG2 cells. This corroborates existing data that GTE hepatotoxicity is a dose-dependent process that induces ROS production, ATP depletion and apoptosis. Regulation of herbal supplements containing this product must be improved to ensure consumer safety and prevent further cases of liver damage.

Mazzanti et al. (2015), Arch Toxicol. 2015;89(8):1175-91

Exploring the TRAIL of doxorubicin-induced cardiotoxicity

Michelle Sims², Giovanni Licari², Romana Panagopoulos², Bill Panagopoulos², Irene Zinonos¹, Benedetta C Sallustio¹,²,³, Andreas Evdokiou¹. Breast Cancer Research Unit, University of Adelaide¹, Adelaide, SA, Australia; Discipline of Pharmacology, University of Adelaide², Adelaide, SA, Australia; Clinical Pharmacology, Central Adelaide Local Health Network³, Woodville South, SA, Australia.

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

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

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

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

Discussion: Our data supports the hypothesis of DOX sensitisation of cardiomyocytes to TRAIL-induced death. Collectively, these findings strongly support TRAIL blockade as a novel therapeutic strategy to limit or eliminate DOX-induced cardiotoxicity and identify several targets for therapeutic intervention.
Ascending Jacob’s Ladder of Density Functional Approximations for in silico toxicological modelling

John Spicer¹, Davy Guan¹, Raymond Lui¹, Slade Matthews¹. Computational Pharmacology & Toxicology Laboratory, Discipline of Pharmacology, School of Medical Sciences, The University of Sydney¹, Sydney, NSW, Australia.

Introduction. The intricate balance between theoretical accuracy and computational cost is a current challenge associated with the use of density functional theory (DFT) methods in the development of quantitative structure activity relationship (QSAR) models. DFT is used to optimise 3D molecular structures and to precisely derive key reactivity descriptors from the molecular orbitals, which are highly applicable for modelling toxicological phenomena. Benchmark studies typically offer researchers guidance on their choice of density functionals by comparison of an often limited number of higher-level theoretical reference values [1].

However, the transferability of these theoretical evaluations to the predictivity and interpretability of resultant QSAR models remain unclear. Aims. This study will explore the predictive performance and interpretability of toxicological QSAR models generated using quantum mechanical (QM) descriptors computed at increasing levels of density functional theory.

Methods. Computation of the single point energies and 21 electronic descriptors of 8,755 chemicals from the Tox21 database [2] will be distributed across the Artemis high performance computing (HPC) cluster and these computations repeated at increasing levels of DFT from HF-3c at the LDA, revPBE, revTPSS, B97, and B2PLYP levels of theory. Multitask deep learning neural network models will be developed for each of the density functionals predicting 68 binary toxicological endpoints, optimised using genetic algorithms with cross- and external-validation, then interpreted using tree manifold and projection (TMAP).

Results. Preliminary results with HPC-distributed HF-3c calculations reduced total computation time from 78h to 3h compared to using a local desktop. Discussion. Improvements in the accuracy of toxicological QSAR models are expected at higher levels of DFT, however, we anticipate a compromise between accuracy gains and exponentially increasing computational costs to ensure these models can be practically utilised for regulatory purposes.

Oral abstracts

100

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

Prof Jeremy K. Nicholson, Murdoch University, Australia.

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

101

Frankenfood and factory farms: Lessons from communicating science in agriculture

Heather J Bray. School of Biological Sciences, University of Western Australia, Perth, WA, Australia.

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

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

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

Nicholas A Buckley1,2. Professor of Clinical Pharmacology, University of Sydney1, Chair, Expert Health Panel for PFAS2

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

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

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

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


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

Ian F Musgrave; School of Medicine, University of Adelaide, Adelaide, SA, Australia.

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

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

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

Communicating quality use of medicines during COVID-19

Darren M Roberts1,2. Clinical Pharmacology and Toxicology, St Vincent’s Hospital, Sydney, NSW, Australia; St Vincent’s Clinical School, University of NSW, Sydney, NSW, Australia.

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

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

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

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

https://covid19evidence.net.au/#living-guidelines
https://www.gradeworkinggroup.org/

Structure and dynamics of class B1 G protein-coupled receptors

Patrick M. Sexton. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville 3052, VIC, Australia.

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

Debbie L Hay1,2. Department of Pharmacology & Toxicology, The University of Otago1, Dunedin, New Zealand; School of Biological Sciences, The University of Auckland2, Auckland, New Zealand.

Amylin is a pancreatic peptide hormone that controls blood glucose and body weight. One amylin mimetic, pramlintide (Symlin), is approved for clinical use for insulin-requiring diabetes but there is substantial scope for improvement by developing other amylin mimetic peptides with improved solubility and extended half-life. Amylin receptors are G protein-coupled receptors (GPCR) but are unusual in that they require accessory proteins, in addition to the core GPCR, to bind amylin with high affinity. Specifically, amylin receptors comprise the calcitonin receptor (CTR), together with receptor activity-modifying proteins (RAMPs). The three RAMPs with CTR form the AMY1, AMY2 and AMY3 receptors, respectively. There are several splice variants of the CTR, and thus there are a large number of amylin receptor subtypes that could contribute to the mechanism of action of amylin. This presentation will outline the pharmacology of amylin receptors, their signalling and what is currently known of how amylin binds and activates its receptors. Challenges with understanding where amylin and its receptors are expressed will be highlighted, as this is crucial for designing receptor subtype-selective drugs. Progress towards the development of novel amylin mimetic peptides will also be discussed.

Fluorescence imaging of peripheral nerves by a Na\textsubscript{v}1.7-targeted inhibitory cystine knot peptide

Christina I. Schroeder1,2, Junior Gonzales3, Paula Demetrio de Souza Franca3,6, Yan Jiang2, Giacomo Pirovano5, Susanne Kossatz4, Navjot Guru1, Dimitry Yarilin3, Akello J. Agwa1,2, Snehal G Patel6,7, Glenn F King2, Thomas Reiner3,8,9,10,11. National Cancer Institute, National Institutes of Health, MD, 21702, USA1, Institute for Molecular Bioscience, The University of Queensland, St Lucia, Queensland 4072, Australia2, Department of Radiology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA3, Department of Otorhinolaryngology and Head and Neck Surgery, Federal University of São Paulo, São Paulo, Brazil4, Molecular Cytology Core Facility, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA5, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA6, Department of Otorhinolaryngology, Weill Cornell Medical College, 1300 York Avenue, New York, NY, 10065, USA7, Department of Surgery, Weill Cornell Medical College, 1300 York Avenue, New York, NY, 10065, USA8, Center for Molecular Imaging and Nanotechnology (CMINT), Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA9, Department of Radiology, Weill Cornell Medical College, 1300 York Avenue, New York, NY, 10065, USA10, Chemical Biology Program, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, 10065, USA11.

Nerve injury is a debilitating condition that more than 20 million Americans live with. Around 25% of nerve injuries arises from surgery and especially during cancer surgery when the tumour tissue surrounding the nerve is distorted. The voltage-gated sodium channel subtype Na\textsubscript{v}1.7, the target for many venom-derived disulfide-rich peptides, has actively been pursued for its involvement in pain, is located on peripheral sensory neurons which are susceptible to injury during surgery. Through fluorescent labelling of peptide Tsp1a, a potent Na\textsubscript{v}1.7 inhibitor from the *Thrixopelma sp.* spider, we can selectively ‘light up’ peripheral nerves at a non-active dose and without side effects (Gonzales et al 2019). This research could potential result in the use of spider-peptides as nerve-imaging agents resulting in fewer nerve injuries during surgery.

Unique mechanisms of GPCR biased signalling by a peptidomimetic agonist of the relaxin receptor RXFP1
Ross AD Bathgate1,2, Martina Kocan1, Adam Valkovic1, Daniel Scott1,2, Brad Hoare1, Shoni Bruell1, Jenny Ju1, Paul R Gooley2, Mohammed Akhter Hossain1. Florey Institute of Neuroscience & Mental Health1, Parkville, Vic, Australia; Department of Biochemistry and Molecular Biology, University of Melbourne2, Parkville, Vic, Australia.

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


Rational design of resistance resistant anti-tuberculosis drugs
David B Ascher1,2,3, Department of Biochemistry, University of Melbourne, VIC, Australia; 2Systems and Computational, Bio21 Institute, VIC, Australia; 3Computational Biology and Clinical Informatics, Baker Heart and Diabetes Institute, VIC, Australia; 4Computational Department of Biochemistry, Cambridge University, Cambridge, UK.

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

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

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

This work has highlighted the potential of using computational and structural insights early in the drug development process. These computational tools are freely available (http://biosig.unimelb.edu.au/biosig/tools), and are being translated in the fight against other infectious and non-infectious diseases.
**110**

**Therapeutic drug monitoring in tuberculosis**

Jan-Willem C Alffenaar. School of Pharmacy, Faculty of Medicine and Health, University of Sydney and Westmead Hospital and Marie Bashir Institute of Infectious Diseases University of Sydney, Sydney, NSW, Australia.

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


**111**

**Bromodomain proteins as potential malaria drug targets**

Michael F Duffy. Department of Microbiology and Immunology, Department of Medicine The Royal Melbourne Hospital, Bio21 Institute, Peter Doherty Institute, The University of Melbourne, Melbourne, VIC, Australia.

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

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

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

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

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

Peter R Carroll1, Jane R Hanrahan1. School of Pharmacy, The University of Sydney, Sydney, NSW, Australia.

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

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

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

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

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

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

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

Chih Yuan Wang1, Alexandra Clavarino2, Sonya Stacey3, Karen Luetsch1. School of Pharmacy1, School of Public Health2, The University of Queensland, Brisbane, QLD, Australia; Children’s Health Queensland Hospital and Health Service3, Brisbane, QLD, Australia.

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

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

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

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

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

William Nguyen1, Claire O’Reilly2, Rebekah Moles3, Jennifer Robinson2, Damianne Brand2, Anne Kim2, Sarira El-Den1. 1School of Pharmacy, Fac of Med and Health, Univ of Sydney1, NSW, Australia; College of Pharmacy and Pharmaceutical Sciences, Washington State Univ2, WA, USA.

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

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

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

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

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

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

Kellie A. Charles1,2, Sarah N Hilmer3,4, Varan Perananthan1,5, Nicholas Buckley1,5. Discipline of Pharmacology SOMS1 Medical Education Unit Sydney Medical School2, Northern Clinical School3, Faculty of Medicine and Health, University of Sydney, and Royal North Shore Hospital3 and Royal Prince Alfred Hospital2, Sydney, NSW, Australia

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

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

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

Suong NT Ngo. School of Animal & Veterinary Sciences, The University of Adelaide, Adelaide, SA, Australia.

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

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

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

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

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

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


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

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

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

Results and Discussion. Phenethyl-ITC reduced viability of transgenic breast cancer cell lines with an 50% inhibitory (IC50) value of 5.48 µM for MCF7, and 5.61 µM for MDA-MB-231. These results are consistent with that reported in the literature (Gutpa 2012). Phenethyl-ITC was also found to inhibit the formation of breast CSC mammospheres, with a decrease in mammospheres’ size and number in both cell lines, although there is potential that the breast CSC may become quiescent rather than being killed. This speculation was based on our further analysis of CSC markers including the pluripotency gene SOX2, and EMT and drug resistance genes (SLUG, VIMENTIN, DNER, and ABCG2) by qRT-PCR, which did not show a clear dose-dependent response to phenethyl-ICT concentrations.

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

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

Results and Discussion. MTT assays show a better anti-proliferative effect with the RSV-encapsulated NP (25% cell viability) than the alternate day for 1 week. However, due to its molecular structure, it undergoes rapid metabolism in the body resulting in very low bioavailability and poor anticancer effect in vivo.

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

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

Yan Jing Yee, Heather AE Benson, Crispin R Dass, Yan Chen. School of Pharmacy and Biomedical Sciences, Curtin Health Innovation Research Institute, Curtin University, Perth, WA, Australia.

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

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

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

Results and Discussion. MTT assays show a better anti-proliferative effect with the RSV-encapsulated NP (25% cell viability) than the RSV-conjugated NP (96% cell viability) at 20 µg/mL RSV equivalent. In the mouse model, the RSV-conjugated NP showed a 33% improvement in suppression of tumour growth compared to mice treated with free RSV, possibly due to its better bioavailability in vivo. This correlates with previous data from in vitro stability studies against metabolism in human microsomes where free RSV and RSV-encapsulated NP degraded by 50% within 40 minutes as opposed to RSV-conjugated NP within 1 hour. This study suggests that chemical conjugation of RSV to an appropriate amphiphilic polymer is a good strategy to improve the therapeutic effectiveness of RSV for melanoma treatment by reducing metabolism of RSV in mice.
120

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

Terrance Lam1, Erica K Sloan1,2,3, Michelle L Halls1. Drug Disc Biol Theme, Monash Inst Pharm Scie1; Monash University, Parkville, VIC, Australia; Cousins Center, UCLA Semel Inst Neurosci and Human Behav and Jonsson Comprehensive Cancer Center, University of California Los Angeles2, California, USA; Div Cancer Surgery, Peter MacCallum Cancer Centre3, East Melbourne, VIC, Australia.

Introduction. Previously, we identified a cAMP-calcium (Ca2+) feedforward loop mechanism in the highly metastatic triple negative breast cancer (TNBC) tumour cell line MDA-MB-231HM (Pon et al, 2016). This mechanism facilitates the dynamic interplay between cAMP and Ca2+ second messenger systems following β2-adrenoceptor activation, to further amplify both signals. Activation of this mechanism facilitates accelerated invasion in MDA-MB-231HM cells.

Aims. To determine the commonality of the β2-adrenoceptor mediated feedforward mechanism amongst a panel of TNBC tumour cell lines and to establish its role in regulating cellular invasion.

Methods. Formoterol was used to activate the endogenously expressed β2-adrenoceptor. Receptor signalling was measured using cAMP accumulation and Ca2+ mobilisation assays in the presence of various inhibitors: adenylyl cyclase (2’,3’-dideoxyadenosine), Goli (pertussis toxin), Gβγ (gallein), protein kinase A (KT5720), exchange protein activated by cAMP (ESI-09), protein kinase C (GF109203X), and Ca2+ chelator (BAPTA-AM). 3D cellular invasion was assessed using microscopy.

Results. Preliminary screening identified three TNBC cell lines which possess elevated cAMP and increased intracellular Ca2+ in response to β2-adrenoceptor stimulation by formoterol; MDA-MB-453 (pEC50 cAMP 8.42 ± 0.25, Ca2+ 7.74 ± 0.27), HCC1806 (pEC50 cAMP 8.39 ± 0.04, Ca2+ 8.70 ± 0.89), HCC1395 (pEC50 cAMP 7.97 ± 0.23, Ca2+ 8.76 ± 0.51). These results provide preliminary evidence for a cAMP/Ca2+ feedforward loop mechanism within these cell lines. Inhibitors were used to delineate any interaction between the cAMP and Ca2+ signalling pathways, and to confirm whether activation of the cAMP/Ca2+ feedforward loop was required to accelerate invasion.

Discussion. The β2-adrenoceptor can accelerate breast cancer progression in response to stress. The feedforward loop may provide strategies to more specifically target this GPCR in order to slow cellular invasion and metastasis.


121

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


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

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

Methods. UGT2B11 and UGT2B28 variants were stably expressed in MDA-MB-453 breast cancer cells. Cellular proliferation was assessed via crystal violet assay and SREBP lipogenic target gene expression was quantified by qPCR. UGT2B11 and UGT2B28 were transiently co-expressed with components of the SREBP signalling complex in a HEK-293T cell model. The stability of nuclear SREBP variants, promoted breast cancer cell proliferation. Gene expression analysis revealed increased levels of multiple SREBP target genes in the UGT-overexpressing cells. Co-expression studies in HEK-293T cells showed that these UGTs can enhance proteolytic turnover of nuclear nSREBPs, leading to reduced transactivation activity.

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

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

Michelle Sims1, Giovanni Licari1, Romana Panagopoulos1, Bill Panagopoulos1, Irene Zinonos1, Benedetta C Sallustio1,2,3, Andreas Evdokiou1. Breast Cancer Research Unit, University of Adelaide1, Adelaide, SA, Australia; Discipline of Pharmacology, University of Adelaide2, Adelaide, SA, Australia; Clinical Pharmacology, Central Adelaide Local Health Network3, Woodville South, SA, Australia.

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

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

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

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

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

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

Isabelle Gillooly1, Edwin Tan1, Rose Cairns1,2. School of Pharmacy, The University of Sydney1, Sydney, NSW, Australia; New South Wales Poisons Information Centre, The Children’s Hospital at Westmead2, Sydney, NSW, Australia.

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

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

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

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

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

Jessy Lim1, Nicholas Buckley2, Kate Chitty2, Rebekah Moles1, Rose Cairns1,2. Sydney Pharmacy School, Faculty of Medicine and Health, University of Sydney1, Sydney, NSW, Australia; Clinical Pharmacology and Toxicology Research Group, Faculty of Medicine and Health, University of Sydney2, Sydney, NSW, Australia.

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

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

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

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

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

Harm from cardiovascular medications: the omitted ‘C’

Chariclia Paradissis1,2, Ian Coombes1,2, Neil Cottrell1, Ian Scott2,3, William Wang2,3, Michael Barras1,2. School of Pharm, Univ of Queensland1, Brisbane, QLD, Australia; Queensland Health2, Brisbane, QLD, Australia; Faculty of Med, Univ of Queensland3, Brisbane, QLD, Australia

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

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

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

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

Discussion. CV medications are a leading cause of medication harm, particularly in older adults, and should be the focus of harm mitigation strategies. A practical approach to generate awareness is to incorporate ‘C’ (for CV medications) into the ‘APINCHS’ acronym. ‘CAPINCH’ (see Figure) would serve as a prompt to optimise the use of CV medications.
The prevalence and characteristics of psychotropic-related hospitalisations in older people: a systematic review and meta-analysis

Ilsa R. Wojt1, Rose Cairns1,2, Alexander Clough1, Edwin C.K. Tan1,3,4
School of Pharmacy, The University of Sydney1, Sydney, NSW, Australia. NSW Poisons Information Centre, The Children’s Hospital at Westmead2, Sydney, NSW, Australia. Centre for Medicine Use and Safety, Monash University3, Melbourne, VIC, Australia. Aging Research Centre, Karolinska Institutet and Stockholm University4, Stockholm, Sweden.

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

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

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

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

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

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

Rebecca J Hertzman1, Kevin DG Pfleger1,2,3,4, Elizabeth KM Johnstone1,2,3.
Mol Endocrinol and Pharmacol, Harry Perkins Inst of Med Res1, Nedlands, WA, Australia; Centre for Med Res, Univ of Western Australia2, Crawley, WA, Australia; Aust Res Council Centre for Personalised Therapeutics Technologies3, Australia; Dimerix Limited4, Nedlands, WA, Australia.

Introduction. The renin-angiotensin system and the kallikrein-kinin system constitute two regulatory systems involved in the maintenance of blood pressure. Interactions between the two systems are numerous and have been extensively studied for decades. The establishment of the concept of G protein-coupled receptor (GPCR) heteromerisation has now revealed new potential interactions between the two systems, including heteromers between the angiotensin type 1 (AT1) and type 2 (AT2) receptors and the bradykinin type 2 (B2) receptor. These receptors form three heteromers whose pharmacology has been investigated to varying extents. We have utilised the recently developed mini G protein biosensors (Wan et al., 2018) to characterise each of the heteromer’s G protein coupling profiles.

Aims. To investigate the G protein coupling pharmacology of the AT1-AT2 heteromer, the AT1-B2 heteromer and the AT2-B2 heteromer.

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

Results. The individual receptors displayed G protein coupling preferences as expected for those receptors. Some novel G protein pharmacology was observed in the heteromer assays, such as ligand-induced G protein recruitment proximal to the AT2 receptor, which does not normally couple to G proteins.

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

A new pertussis toxin-like protein complex as a tool for investigation of GPCR-Gαi and Gαz signalling
Alastair C Keen1,2, Maria H Pedersen3, Jonathan A Javitch3, J Robert Lane2. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University1, Melbourne, VIC, Australia; Cell Signalling & Centre of Membrane Proteins and Receptors (COMPARE), School of Life Sciences, University of Nottingham2, Nottingham, United Kingdom; Departments of Psychiatry and Pharmacology, Columbia University3, New York, NY, United States.

Introduction. AB5 toxins such as pertussis toxin are heterohexameric protein complexes secreted by pathogenic bacterial species. The B subunits of AB5 toxins bind host cell surface receptors and provide entry to the cells. The catalytically active A subunit then acts on intracellular proteins to modify cell signalling and cell behaviour. Due to their actions, AB5-type toxins have become useful tools for delineating intracellular signalling pathways and understanding cellular processes. Recently, a novel pertussis toxin-like family AB5 toxin was identified and characterised (Littler et al, 2017). The toxin was reported to act similarly to pertussis toxin by ADP-ribosylating heterotrimeric G proteins preventing their interaction with and activation by G protein coupled receptors. It was, however, shown to act at a structurally distinct amino acid site on the G protein.

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

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

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

Discussion. This new toxin may be used as a tool in combination with pertussis toxin for understanding the function of inhibitory family heterotrimeric G proteins including Gαz. This study warrants further investigations into unexplored AB5 toxins in an effort to find more molecular tools.


Differential G protein activation kinetics may underpin the beneficial aspects of clinically trialled A1R atypical agonists
Samantha M McNeill1, Jo-Anne Baltos1, Nevin Lambert2, Paul J White3, Lauren T May1. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences1, Melbourne, VIC, Australia; Medical College of Georgia, Department of Pharmacology and Toxicology, Augusta University2, Augusta, GA, USA.

Introduction. Activation of adenosine A1 receptors (A1Rs) represents a powerful strategy for the treatment of cardiovascular disease. Clinically trialled atypical A1R agonists, capadenoson and neladenoson, stimulate cardioprotection (Sabah et al, 2013) with minimal bradycardia (Shah et al, 2019; Sabah et al, 2013), a signalling profile typically attributed to reduced intrinsic efficacy. However, capadenoson and neladenoson are biased A1R agonists (Baltos et al, 2016; Rueda et al, 2020), and as such a better mechanistic understanding is required to facilitate the rational design of more effective A1R therapeutic candidates. Aim. To quantify A1R-mediated Gβγ-effector interactions in response to prototypical and atypical A1R agonists; as Gβγ-GIRK channel interactions are the direct mechanism for A1R-mediated bradycardia. Methods. Stably expressing A1R-HEK293A cells with all G proteins deleted were transiently transfected with masGRKct-nanoluc, Gαoa, and Gβ1γ2-venus. The masGRKct construct readily binds free Gβγ dimers, on a timescale that mirrors GIRK channel activation (Hollins et al, 2009). Results. The prototypical agonist MeCCPA and capadenoson were equipotent with a similar maximal response (pEC50: 6.6 – 6.9; n=3-4, P>0.05). However, the onset kinetics of Gβγ-effector interactions atypical agonists were significantly reduced by 4-8 fold as compared to prototypical agonists (n=3-4, P<0.05). Discussion. Considering the similar potency and maximal response observed for MeCCPA and capadenoson, the different kinetic profile of Gβγ-effector interactions may have a key role in conferring the clinically beneficial profile of atypical A1R agonists.

The structural basis for the UDP-sugar selectivity of human UDP-glycosyltransferase 2B7 (UGT2B7): A combined computational and experimental approach.

Pramod C Nair¹, Nuy Chau¹, Ross A McKinnon¹ and John O Miners¹. Department of Clinical Pharmacology, Flinders Health and Medical Research Institute, Flinders University College of Medicine and Public Health¹, Adelaide, SA, Australia.

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

Aims. 1) Identify key residue(s) associated with the selective binding of UDP-GlcUA over UDP-Glc using molecular dynamics simulations (MDS). 2) Experimentally validate the observations from MDS using site-directed mutagenesis (SDM) and enzyme activity assays.

Methods. Molecular dynamics simulations were performed with a UGT2B7 homology model. UDP-GlcUA and UDP-Glc were docked in the cofactor binding site of the protein. The Arg259Leu mutant was generated by SDM. Enzyme kinetic studies were performed on wild-type UGT2B7 and the Arg259Leu mutant using zidovudine, morphine and 4-methylumbelliferone as the substrate probes. Results. MDS demonstrated that multiple residues in the C-terminal domain of UGT2B7 stabilise the binding of both UDP-GlcUA and UDP-Glc. However, Arg259 in the N-terminal domain additionally forms a salt-bridge and H-bonds with UDP-GlcUA, whereas no interactions were noted between Arg259 and UDP-Glc. Wild-type UGT2B7 glucuronidated all three probe substrates, but the Arg259Leu mutant lacked glucuronidation activity. By contrast, morphine 3-glucosidation formation was unaffected by the Arg259 to Leu substitution.

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

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

Jessica J Lu¹, Peishen Zhao¹, Patrick M Sexton¹, Denise Wootten¹. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences¹, Parkville, VIC, Australia

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

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

Methods. PAC1R isoforms and TRUPATH biosensors were transiently transfected into COS-7 cells and treated with increasing concentrations of agonists: PACAP-38, PACAP-27, vasoactive intestinal peptide (VIP) and maxadilan. Real-time G protein dissociation profiles of Gs, Gi, Gq/11, and G12 were measured at 37°C using PHERAstar (BMG Biotech).

Results. Insertions in ICL3 altered the G-protein coupling profiles of PAC1n and PAC1s. PAC1n-hop displayed a four-fold increase in PACAP-38 potency for Gq/11 coupling (Gq pEC50: 8.4±0.1; G12 pEC50: 8.3±0.1) compared to PAC1n (Gq pEC50: 7.8±0.2; G12 pEC50: 7.8±0.2). While, insertions of the hip and hiphop cassettes led to weaker Gi coupling. PAC1s increased the potency of VIP-mediated G protein coupling for all four G protein subtypes.

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

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

Jackie Hunter, BenevolentAI, UK

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

Plant with the scorpion sting: pharmacology of Australia’s most venomous plant “Gympie-Gympie”

Jennifer R. Deuis¹, Edward K. Gilding², Sina Jami¹, Mathilde R. Israel¹,², Peta J. Harvey¹, Aaron G. Poth¹, Fabian B.H. Rehm¹, Jennifer L. Stow¹, Samuel Robinson¹, Glenn F. King¹, Kuok Yap¹, Darren L. Brown¹, Brett R. Hamilton¹, David Andersson³, David J. Craik¹, Irina Vetter¹,⁴, Thomas Durek¹. Institute for Molecular Bioscience, The University of Queensland¹, Brisbane, QLD, Australia. Institute of Psychiatry, Psychology & Neuroscience, King’s College London², London, United Kingdom. Centre for Advanced Imaging, The University of Queensland³, Brisbane, QLD, Australia. School of Pharmacy, The University of Queensland⁴, Brisbane, QLD, Australia.

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

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

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

Results. Application of ExTxA (100 nM) to the receptive fields of mechanosensitive A- and C-fibers caused spontaneous action potential (AP) firing, confirming direct activation of primary sensory neurons. ExTxA (10 nM) caused Ca²⁺ influx in the majority of neurons (68%) that was significantly reduced (26%) by tetrodotoxin (TTX; 1 μM), suggesting activity at voltage-gated sodium channels (NaV). Indeed, ExTxA potently and irreversibly delayed fast inactivation of voltage-gated sodium channels (EC₅₀ 58 nM), providing a pharmacological basis for sting-induced pain.

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

Eryn L Werry1,2, Samuel Lane3, Erick C.N. Wong3, Alexander Shaw3, Loyola McLean3, Caryl Barnes3, Rachael Holt3, Trudy Stone3, Cynthia Forlini3, Louise Nash1. Faculty of Medicine and Health1; Faculty of Science2, The University of Sydney, NSW, Australia; Faculty of Health3, Deakin University, VIC, Australia

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

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

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

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

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

Global solutions to global challenges-prioritising our efforts

Prof Parisa Aslani, The University of Sydney, NSW, Australia
Biased negative allosteric modulators for the calcium-sensing receptor have differential bronchodilator and bronchoprotective effects in mouse precision cut lung slices

Jiayin Diao1, Maggie Lam2, Karen Gregory1,2, Katie Leach1,2, Jane E. Bourke2. 1Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash Uni, Parkville; 2Biomed Discovery Institute, Monash Uni., Clayton, VIC, Australia.

Introduction. The calcium-sensing receptor (CaSR) detects changes in extracellular calcium (Ca2+) to maintain Ca2+ homeostasis. The CaSR is upregulated in asthma, and CaSR negative allosteric modulators (NAMs) reduce inflammation, remodelling, and airway hyperresponsiveness in a mouse model of chronic allergic airways disease (Yarova et al, 2015). Whether CaSR NAMs, which engender biased modulation (Davey et al, 2012), have different bronchodilator and/or bronchoprotective effects is unknown.

Aim. To assess CaSR NAM (NPS2143, Pfizer cmpd 1, BMS cmpd 1) bias in CaSR-HEK293 cells and compare NAMs with the β2-adrenoceptor agonist salbutamol for airway relaxation.

Methods. Intracellular calcium (Ca2+) mobilisation and IP3 accumulation assays in CaSR-HEK293 cells were used to quantify the affinity and cooperativity of CaSR NAMs. Precision cut lung slices from male C57Bl/6 mice were prepared to visualise changes in airway area after contraction stimulated by 300 nM methacholine (MCh) followed by NAM or salbutamol (bronchodilation assays) or after overnight pre-incubation with 1 μM NAMs (bronchoprotection assays).

Results. CaSR NAMs engendered differential and biased modulation of Ca2+ mobilisation and IP3 accumulation. CaSR NAMs relaxed pre-contracted airways in a biphasic manner (see figure), with the highest potency first phase of their response being 1000-fold higher potency than salbutamol. Salbutamol and NAMs caused comparable maximal bronchodilation (salbutamol 50±7%, NPS2143 32±8%, Pfizer cmpd 1 70±16%, BMS cmpd 1 48±16%, n=4-6). Overnight incubation with NPS2143 and Pfizer cmpd 1, but not BMS cmpd 1 prevented contraction.

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


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

Yifan Huang1, Mark D Habgood2, Fiona Qiu1, Samuel J Toll1, Katarzyna M Dziegielew ska1, Norman R Saunders1. Department of Pharmacology and Therapeutics, The University of Melbourne1, Melbourne, VIC, Australia.

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

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

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

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

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

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

Yifang Li1, Matthew Shen1, Dorota Ferens2, Brad R.S. Broughton1, Padma Murthi1, Robert E. Widdop1, Sharon D. Ricardo1, Anita A. Pinar1, Christan S. Samuel1, Department of Pharmacology, Monash University1, Clayton Victoria 3800, Australia.

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

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

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

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

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

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

Kevin Mou1, Stanley MH Chan1, Kurt Brassington1, Aleksandar Dobric1, Simone N. De Luca1, Huei Jiunn Seow1, Ross Vlahos1. School of Health & Biomedical Sciences, RMIT University1, Bundoora, VIC, Australia.

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

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

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

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

Discussion. Acute IAV infection per se specifically impaired muscle function without muscle loss. This suggests that muscle function may be more vulnerable to IAV infection than muscle mass. The lack of an additive effect may imply the involvement of mechanisms other than simple lung inflammation in driving the observed muscle dysfunction.
**207**

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

Margaret A Mouat1,2,3, Kristy L Jackson4, James LJ Coleman1,3, Madeleine R Paterson5, Robert M Graham1,3, Geoff A Head4, Nicola J Smith1,2,3. Molecular Cardiology and Biophysics Div, Victor Chang Cardiac Research Institute1, Sydney, NSW, Australia; Department of Pharmacology, UNSW2, Sydney, NSW, Australia; St Vincent’s Clinical School, UNSW3, Sydney, NSW; Neuropharmacology Laboratory, Baker Heart and Diabetes Institute4, Melbourne, VIC, Australia.

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

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

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

Results. GPR37L1-/- genotype had a statistically significant positive effect on HR across both sexes (genotype effect p=0.0002, two-way ANOVA). Both sexes of GPR37L1-/- mice exhibited attenuated depressor responses to ganglionic blockade, indicating reduced sympathetic vasomotor tone. There was a reduction in the night-time HR power spectra of female GPR37L1-/- mice within a frequency band correlated with vagal drive. Interestingly, female GPR37L1-/- mice exhibited an attenuation of cardiovascular reactivity to stress compared with controls. The attenuation was observed in both the male and female GPR37L1-/- mice.

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

**208**

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

Anida Velagic1, Jasmin Chendi Li1, Chengxue Qin1, Mandy Li2, Minh Deo1, Sarah A Marshall3, Owen L Woodman1, John D Horowitz4, Barbara K Kemp-Harper5, Rebecca H Ritchie1-2. Depts of Drug Discovery Biology1, Pharmacology2 and Obstetrics and Gynaecology3, Monash Univ, Clayton, VIC; Queen Elizabeth Hospital, Univ of Adelaide, SA.

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>DEA/NO (10^{-5} M)</th>
<th>Angeli’s salt (10^{-5} M)</th>
<th>Insulin (33.3 IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ND (n=8)</td>
<td>Diabetic (n=8)</td>
<td>ND (n=8)</td>
</tr>
<tr>
<td>∆LVDP (mmHg)</td>
<td>5.7±0.7</td>
<td>2.3±0.6*</td>
<td>4.1±0.7</td>
</tr>
<tr>
<td>∆LVDP (mmHg)</td>
<td>2.6±0.6</td>
<td>1.1±0.2*</td>
<td>1.8±0.3</td>
</tr>
<tr>
<td>∆LV+dp/dt (mmHg/s)</td>
<td>147±19</td>
<td>96±18*</td>
<td>121±11</td>
</tr>
<tr>
<td>∆LV-dp/dt (mmHg/s)</td>
<td>-133±18</td>
<td>-78±7*</td>
<td>-102±13</td>
</tr>
<tr>
<td>∆Coronary flow (mL/min)</td>
<td>7.0±0.7</td>
<td>4.6±0.9*</td>
<td>6.5±0.7</td>
</tr>
<tr>
<td>∆Heart rate (bpm)</td>
<td>14.5±2.3</td>
<td>21.2±1.3*</td>
<td>9.6±1.0</td>
</tr>
</tbody>
</table>

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

Discussion. These findings demonstrate for the first time that the HNO donor Angeli’s salt circumvents NO• resistance in the diabetic insulin-resistant myocardium, highlighting the therapeutic potential of HNO donors to treat acute diabetes-associated impairments in cardiac function.
Predictive performance of population pharmacokinetic models for tacrolimus in lung transplant recipients


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

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

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

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

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

Intracellular enzymatic activation of 4-hydroxycylophosphamide in leukocytes.

Minghan Yong, Nuala A Helsby, Kathryn E Burns, Janak de Zoysa. Department of Molecular Medicine and Pathology, University of Auckland; North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand.

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

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

Methods. Purified DNA or peripheral blood mononuclear cells (PBMC) were incubated with 4-OHCP or PAM. The amount of DNA alkylation in the template DNA was quantified by QPCR-block assay. Data from replicate experiments were plotted as IC50 curves. A low IC50 indicates high DNA alkylation. Incubation with snake venom PDE and purified human PDE isoforms were used to determine if these enzymes activate 4-OHCP.

Results. 4-OHCP was a weak alkylator of purified DNA compared to PAM (IC50 >1000 µg/mL vs 0.554 µg/mL). In contrast, in PBMC 4-OHCP alkylated DNA to a greater extent than PAM (IC50 61.5 µg/mL vs 186 µg/mL). Snake venom PDE and human recombinant PDE4B2 activated 4-OHCP into an alkylating agent (47% and 41% increase respectively, P<0.05).

Discussion. This data indicates that leukocytes and PDE can activate 4-OHCP into the DNA reactive product important for its mechanism of action in autoimmune disease.
The Influence of Haemostatic System Maturation on the Dose-Response Relationship of Unfractionated Heparin

Abdallah Derbalah1, Stephen Duffull1, Katie Moynihan2, Hesham All-Sallami1. School of Pharmacy, University of Otago1, Dunedin, Ota, New Zealand; Department of Cardiology, Boston Children’s hospital2, Boston, MA, United States.

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

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

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

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

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


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

Christopher B Cunio1,2, David W Uster3, Jane E Carland7, Hergen Buscher4, Zhixin Liu5, Jonathan Brett1, Maurizio Stefani2, Graham R D Jones9, Richard O Day1,2, Sebastian G Wicha3, Sophie L Stocker1. Dept of Clin Pharmacol & Toxicol, St Vincent’s Hosp (SVH)1, Sydney, NSW, Australia; Sch of Med Sci2, UNSW, Sydney, NSW, Australia; Dept of Clin Pharm, Inst of Pharm, Univ of Hamburg4, Hamburg, HH, Germany; Dept. of Intensive Care Medicine, SVH5, Sydney, NSW, Australia; Stats Central, UNSW6, Sydney, NSW, Australia; SydPath, SVH7, Sydney, NSW, Australia

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

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

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

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

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

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

Varan Perananthan1,2,3, Thilini Wijeyrathna2, Mohamed Fahim4, Indika Gawarammana2, Andrew Dawson1,2,3, Nicholas A Buckley1,2,3. Drug Health Services, Royal Prince Alfred1, Sydney, NSW, Australia; South Asian Clinical Toxicology Research Collaboration2, Peradeniya, Sri Lanka; Department of Pharmacology3, University of Sydney, Sydney, NSW, Australia.

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

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

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

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

Quality analysis of commercially available Annona muricata leaf products

Wai-Jo J Chan1, Joanna E Harnett1, Andrew J McLachlan1, Jane Hanrahan1, School of Pharmacy, Faculty of Medicine and Health1, Sydney, NSW, Australia.

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

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

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

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

Discussion. The variation in product quality and safety indicators raises significant considerations for clinicians and people living with cancer about the safe use of traditional medicine products.
Apocynin ameliorates cigarette smoking-induced loss of skeletal muscle mass and function by preserving protein synthesis signalling.

Stanley MH Chan, Ivan Bernardo, Chanelle Mastronado, Kevin Mou, Simone N De Luca, Huei Jiunn Seow, Aleksandar Dobric, Kurt Brassington, Stavros Selemidis, Steven Bozinovski, Ross Vlahos

School of Health and Biomedical Sciences, RMIT University, BUNDOORA, VIC 3083, Australia

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

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

Methods. Male BALB/c mice were exposed to either room air (sham) or CS generated from 9 cigarettes per day, 5 days per week for 8 weeks with or without apocynin (5mg·kg⁻¹·day⁻¹, i.p. injection) administration. C2C12 myotubes exposed to either hydrogen peroxide (H₂O₂, 0-100μM) or water-soluble cigarette smoke extract (CSE, 0-100%) with or without apocynin (500 nM), was set up as an experimental model in vitro.

Results. In mice, 8 weeks of CS exposure resulted in lung inflammation and muscle dysfunction evidenced by a 10% loss in mass and 54% loss (both p<0.01, n=8) in contractile function of tibialis anterior. The muscle dysfunction is likely to be attributed to a combination of altered myogenic homeostasis and protein oxidation. These effects were largely ameliorated by apocynin administration (p<0.05, n=8). In C2C12 myotubes, exposure to H₂O₂ or CSE led to myofiber wasting in a concentration-dependent manner. The myofiber wasting was associated with altered protein synthesis signalling marked by ~50% loss in muscle-derived Insulin-like growth factor (IGF)-1 and 1.5-fold increase in myostatin expression (p<0.01, n=3) without muscle inflammation. Apocynin treatment completely attenuated the CSE-induced NADPH oxidase 2 expression, preserving muscle-derived IGF-1 expression and downstream mTOR signaling pathway, thereby protecting the myofibers against wasting (p<0.01, n=3).

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

Spatial reference memory impairment is augmented in hypertensive mice following stroke

David E. Wong Zhang, Grant R. Drummond, Christopher G. Sobey & T. Michael De Silva. Department of Physiology, Anatomy and Microbiology, La Trobe University, Melbourne, VIC, Australia.

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

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

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

Discussion. These findings indicate that the combination of hypertension and stroke resulted in more severe spatial reference memory impairment and brain injury than either insult alone.
Relaxin inhibits matrix remodelling of collagen gels by asthmatic fibroblasts

Maggie Lam1, Frank A Cirnigliaro1, Katherine Martin1, Simon G Royce2, Belinda Thomas2, Chrishan S Samuel1, Philip Bardin2, Jane E Bourke1. Dept of Pharmacology, Monash University, Clayton, VIC, Australia1 Hudson Institute of Medical Research, Clayton, VIC, Australia2

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

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

Methods. Non-asthmatic and asthmatic fibroblasts were serum-starved for 72h before experiments. Cells were trypsinized and resuspended at 0.5x10⁶ cells/mL in 4X DMEM and combined with collagen solution (1 part cells: 3 part collagen). This mixture was transferred into 24-well culture plates (500 µL/gel). Once set, gels were dislodged into 6-well culture plates and suspended in 3 mL 1xDMEM for up to 72 h. Gels were treated with TGFβ (2ng/ml) in the absence and presence of RLX (100nM), and compared to pirfenidone (500µM) and dexamethasone (100nM).

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

Discussion. RLX opposes the increased contraction of collagen gels by TGFβ1 more effectively than pirfenidone or dexamethasone. These promising results, also evident in gels seeded with non-asthmatic fibroblasts, support the potential role of RLX in asthma and its inhibitory effect was more marked in SHR than WKY rats.

Anandamide-induced vasodilatation in normotensive and hypertensive rats

Daria Kornienko, Makhala M Khammy. Dept of Pharmacol, Univ of Melbourne, Parkville, VIC, Australia

Introduction. Anandamide, an endogenous agonist of cannabinoid CB1 receptors and transient receptor potential vanilloid 1 (TRPV1) channels, can inhibit vasoconstriction and decrease blood pressure by modulating sympathetic and sensory neurotransmission. The effect of anandamide action on vascular tone in hypertension is unclear.

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

Methods. In anaesthetised rats (2% isoflurane mixed with O2; spontaneous inhalation via nose cone), intravital microscopy was used to investigate mesenteric arterial diameter. Anandamide concentration-response curves were generated in U46619-constricted (300 nmol/L) arteries from both rat groups. Anandamide concentration-response curves were generated in U46619-constricted (300 nmol/L) arteries in the absence and presence of i) the CGRP receptor antagonist, BIBN 4096 (1 µmol/L); ii) the fatty acid amide hydrolase (FAAH) inhibitor, URB937 (1 µmol/L); and iii) capsaicin (10 µmol/L) to desensitise sensory nerves. Similar experimental protocols were performed in isolated mesenteric arteries via wire myography.

Results. Anandamide caused concentration-dependent relaxation in arteries from both rat groups. Maximum relaxation (Rmax) was greater in WKY rats than in SHR (89±9 vs. 47±5%, n=7 and 6, respectively; P<0.05). URB937 enhanced anandamide-mediated vasodilatation in SHR only (Rmax, 89±6%, n=5; P<0.05). Capsaicin abolished anandamide-mediated relaxation in both groups (Rmax, 1±6 and 11±8%, respectively, n=5; P<0.05) while BIBN 4096 had no effect. In contrast, in vitro anandamide relaxed pre-constricted mesenteric arteries isolated from WKY rats and SHR with similar potency and efficacy (pEC50, 6.22±0.04 vs. 6.31±0.05, respectively) and URB937 had no appreciable effect on anandamide-mediated relaxation. Capsaicin inhibited anandamide-mediated relaxation in vitro and its inhibitory effect was more marked in SHR than WKY rats (63-fold vs. 23-fold decrease in pEC50, respectively; P<0.05).

Discussion. Compared to WKY rats, anandamide-mediated relaxation was impaired in SHR in vivo, possibly due to a higher level of expression and/or activity of FAAH in SHR arteries. Although the inhibitory effects of capsaicin initially suggest the involvement of sensory nerve activation in anandamide-mediated vasodilatation, the absence of inhibition following BIBN 4096 treatment suggests that sensory nerve-derived CGRP is not involved in anandamide-mediated vasodilatation in vivo. In contrast to arteries in the intact circulation, FAAH activity may be limited in isolated arteries.
The pro-resolving lipid mediator lipoxin A4 protects against inflammation in diabetic cardiomyopathy

Ting Fu1,2, Minh Deo2, Muthukumar Mohan4, Madura Bose4, Eoin Brennan5, Catherine Godson5, Phillip Kantharidis4, Rebecca H Ritchie1,3,4,5, Chengxue Qin1,3,4,5,1. Dept of P&T, Univ of Melbourne, VIC; 2Dept of DDB, 3 Dept of Diabetes, Monash Univ, VIC; 4Baker IDI, VIC, Australia; 5UCD DCRC, Univ College Dublin, Dublin, Ireland.

Introduction. Failure to resolve inflammation may contribute to the progression of diabetic cardiomyopathy. We have previously demonstrated that the pro-resolving lipid mediator lipoxin A4 (LXA4) attenuates the development and progression of diabetes-induced atherosclerosis, but its impact on diabetic hearts has not been fully explored.

Aim. To test the hypothesis that LXA4 could attenuate cardiac inflammation in diabetic mice.

Methods. 6-week-old male ApoE−/− mice were followed for 16wks after streptozotocin (55mg/kg/day i.p. for 5 days)-induced diabetes or vehicle control. Mice were randomly allocated to receive either LXA4 (5μg/kg) or vehicle (0.02% ethanol) via i.p. injections twice/week for the final 6wks. At the end of the study, mice were culled with an overdose of Sodium Pentobarbital (100mg/kg), organs harvested for ex-vivo analysis.

Results. Diabetic mice displayed elevated HbA1c levels, retarded body weight gain, increased infiltration of macrophages in the myocardium and elevated expression of M1-like macrophage marker Il-1β. The macrophages content was no longer evident in the diabetic mice treated with LXA4.

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetic mice</th>
<th>Diabetic mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>LXA4</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>32.06±1.78 (n=17)</td>
<td>30.63±2.50 (n=8)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.55±0.58 (n=15)</td>
<td>4.56±0.52 (n=15)</td>
</tr>
<tr>
<td>Macrophage content (No./0.43mm²)</td>
<td>11.73±4.04 (n=13)</td>
<td>12.39±4.31 (n=12)</td>
</tr>
<tr>
<td>mS100A9 (fold increase)</td>
<td>1.00±1.92 (n=17)</td>
<td>0.49±0.31 (n=7)</td>
</tr>
<tr>
<td>mIl-16 (fold increase)</td>
<td>1.00±0.95 (n=17)</td>
<td>0.92±0.37 (n=7)</td>
</tr>
</tbody>
</table>

**p<0.001, ****p<0.0001 vs non-diabetic + vehicle; 2-way ANOVA, Fisher’s post-hoc for multiple comparisons).

Conclusion. LXA4 may reduce inflammation by promoting the resolution of inflammation in the diabetic heart, thus supporting the development of an LXA4 based therapy to improve the outcome for patients with diabetic heart diseases.

Ebselen prevents cigarette smoke-induced cognitive impairment in mice.

Simone N. De Luca3, Kurt Brassington1, Aleksandar Dobric1, Stanley Chan1, Huei Jiunn Seow1, Kevin Mou1, Ross Vlahos3. 1School of Health and Biomedical Sciences, RMIT University, Melbourne, VIC, Australia.

Introduction. Chronic obstructive pulmonary disease (COPD) is a major, incurable health burden, that is currently the 3rd leading cause of death globally, with cigarette smoking (CS) being the leading causative factor. People with COPD often suffer from cognitive dysfunction.

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

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

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

Discussion. Chronic CS exposure impairs hippocampal-dependent memory which was associated with neuroinflammation and oxidative stress. By targeting oxidative stress, ebselen ameliorated CS-induced neuroinflammation, which completely prevented memory loss. Ebselen may be a novel therapeutic treatment for the neurocognitive impairments associated with COPD.
The psychosocial and work related impacts of the COVID-19 pandemic on Australian Pharmacists
Karlee Johnston1. Medical School, Australian National University1, Canberra, ACT, Australia

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

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

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

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

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


Do pharmacy practice standards effectively describe behaviour? Reviewing practice standards using a behavioural specificity framework
Deanna Mill1 Danielle D’Lima2 Amy Page1,3,4 Jacinta Johnson5,6 Kenneth Lee1 Sandra Salter1 Liza Seubert1 Rhonda Clifford1. School of Allied Health UWA1, Perth, WA, Australia; CBC, Dept of Clin, Ed and Health Psych, UCL2, London, United Kingdom; CMUS, Monash Univ3 Pharmacy Dept, The Alfred4, Melbourne, VIC, Australia; UniSA Clin and Health Sci, UniSA5, SA Pharmacy, SA Health6, Adelaide, SA, Australia

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

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

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

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

Discussion. The successful development of a novel reproducible process and codebook to evaluate behavioural specificity could be used by practice standard and guideline developers in the pharmacy profession, and beyond, to improve interpretability, useability and adherence to these documents.
Expanding primary health care pharmacy practice in Aotearoa New Zealand: testing theories using a realist-informed approach

Tara Officer1, Caroline Morris2, Janet McDonald1, Ausaga Fa’aasalele Tanuvasa1, Kirsten Smiler1, Lynne Russell1, Jane McCormack1, Jacqueline Cumming1, Health Services Research Centre, Victoria University of Wellington1, Wellington, NZ; Department of Primary Health Care and General Practice, University of Otago2, Wellington, NZ

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

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

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

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

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

Interprofessional collaboration of general practice pharmacists in the Australian Capital Territory

Thilini Sudeshika1,2, Louise Deeks3, Gregory Peterson1,3, Mark Naunton1, Sam Kosari1, Discipline of Pharmacy, Faculty of Health, Univ of Canberra1, Bruce, ACT, Australia; Dept of Pharmacy, FAHS, Univ of Peradeniya2, Peradeniya, Sri Lanka; School of Pharmacy and Pharmacol, Univ of Tasmania3, Hobart, TAS, Australia.

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

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

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

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

Discussion. Overall, the results indicate that pharmacists were positively interacting with both GPs and OHPs after commencing their role in the general practice team. The interdependence of roles and trust towards general practice pharmacists appeared to be greater with OHPs than GPs.
Pharmacists’ roles in supporting people living with severe and persistent mental illness: a systematic review

Ricki Ng1, Sarira El-Den1, Amanda J Wheeler2–3, Sara S McMillan1, Claire L O’Reilly1. Sydney Pharmacy School, The University of Sydney1, Sydney, NSW, Australia; Menzies Health Institute, Griffith University2, Nathan, Queensland, Australia; Faculty of Health and Medical Science, University of Auckland3, Auckland, New Zealand

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

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

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

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

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

Are Australian community pharmacists engaging in mental health promotion?

Oliver Watt1, Fiona Kelly1, Vijay Suppiah2, Elizabeth Hotham2, Amanda J Wheeler3, Sara S McMillan1. School of Pharmacy and Pharmacology, Griffith University,1 Gold Coast, QLD, Australia; Clinical and Health Sciences, University of South Australia2, Adelaide, SA, Australia; School of Human Services and Social Work, Griffith University3, Brisbane, QLD, Australia.

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

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

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

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

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

Sarah N Hilmer1. Departments of Clinical Pharmacology and Aged Care, Royal North Shore Hospital and Kolling Institute, Faculty of Medicine and Health, University of Sydney1, Sydney, NSW, Australia.

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

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

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

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

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

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

Prof Tina Brock, Monash University

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

Nagham J Ailabouni1, Emily Reeve1, Dorsa Maher1, Tuan Nguyen1, Sarah N Hilmer2, Prasad S Nishtala3 University of South Australia, UniSA: Clinical & Health Sciences, Adelaide, SA1 University of Sydney, Kolling Institute of Medical Research, Sydney, NSW2 University of Bath, Department of Pharmacy and Pharmacology, Bath, England3

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

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

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

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

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

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

Edwin CK Tan1, Alexander J Clough1, Danijela Gnjidic1,2. The University of Sydney School of Pharmacy, Faculty of Medicine and Health1, Sydney, NSW, Australia; The University of Sydney, Charles Perkins Centre2, Sydney, NSW, Australia.

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

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

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

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

Discussion. Preliminary findings suggest that the quality of care of Australians with dementia in general practice could be improved with regard to documentation of dementia and its specific subtypes.
231

Older adult and caregiver attitudes towards deprescribing: a systematic review

Kristie R Weir, Nagham J Ailabouni, Sarah N Hilmer, Emily Reeve. Clinical and Health Sciences, Univ of South Australia, UniSA Adelaide, SA, Australia; Kolling Inst, Royal North Shore Hosp and Sydney Univ, St Leonards, NSW

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

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

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

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

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

232

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

Mouna Sawan, Mitchell Redston, Linda Koria, Sarah N Hilmer, Danijela Gnjidic. Syd Pharm School, Faculty of Med and Health, Univ of Sydney, NSW, Australia; School of Medicine, Univ of Notre Dame, Darlinghurst, NSW, Australia; Depts of Aged Care and Clin Pharmacol, Kolling Institute of Medical Research, Royal North Shore Hosp and Northern Clin School, Faculty of Med and Health, Univ of Sydney, Sydney, NSW, Australia;

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

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

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

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

Discussion. Among inpatients with dementia, almost half are exposed to polypharmacy and PIMs. Future studies are needed to evaluate prescribing patterns across services to identify targets for interventions.
Tools to evaluate medication management for caregivers of people with dementia: a systematic review

Melissa Gench1, Mouna J Sawan1, Aili Langford1 & Danijela Gnjidic1,2. School of Pharmacy, Faculty of Medicine and Health, The University of Sydney1, Sydney, NSW, Australia; Charles Perkins Centre, The University of Sydney2, Sydney, NSW, Australia

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

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

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

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

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

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

Ryan J. Keenan1, Heather Daykin1,2, Linda Cornthwaite-Duncan1, Jiahui Chu1, Giancarlo Allocca1,2, Daniel Hoyer1,2,3 and Laura H. Jacobson1,2. 1Department of Pharmacology and Therapeutics, FMDHS, The University of Melbourne, Parkville, VIC, Australia. 2 Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia. 3 Department of Molecular Medicine, The Scripps Research Institute, La Jolla, CA, USA.

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

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

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

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

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

Effects of β-estradiol on porcine distal ureteral contractility

Iris Lim¹, Caio Christiansen¹, Russ Chess-Williams¹. Centre for Urology Research, Bond University¹, Gold Coast, QLD, Australia.

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

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

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

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

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


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

Natasha C Dale¹,²,³, Elizabeth KM Johnstone¹,²,³, Kevin DG Pfleger¹,²,³,⁴. Mol Endocrinol and Pharmacol, Harry Perkins Inst of Med Res¹, Nedlands, WA, Australia; Centre for Med Res, Univ of Western Australia², Crawley, WA, Australia; Aust Res Council Centre for Personalised Therapeutics Technologies³, Australia; Dimerix Limited⁴, Nedlands, WA, Australia.

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

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

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

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

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

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

KH Christopher Choy1*, Emma T van der Westhuizen1*, Peik Jinn Chong1, Luke Williams1, Elham Khajehali1, Nicholas Barnes1, Simon McKenzie-Nickson1, Celine Valant1, Patrick M Sexton1, Andrew B Tobin2, Arthur Christopoulos1. Drug Discovery Biology, Monash Institute for Pharmaceutical Sciences1, Monash University, Parkville, VIC, Australia; Institute of Molecular Cell & Systems Biology, University of Glasgow2, Glasgow, Scotland. *Denotes co-first authors.

Introduction. The M4 muscarinic acetylcholine receptor (mACHR) is a novel target for the treatment of schizophrenia (Gould et al., 2018), and can be selectively targeted with positive allosteric modulators (PAMs) to increase the sensitivity of the receptor to its endogenous neurotransmitter, acetylcholine, ACh. M4 PAMs can enhance the affinity and/or efficacy of ACh and boost the cholinergic system. Through recent extensive medicinal chemistry efforts, a plethora of M4 selective PAMs has been identified, with one particularly promising compound, VU0467154.

Aim. To pharmacologically assess the novel M4 PAM, VU0467154, in recombinant systems overexpressing the human or the mouse M4 mAChRs, and in two mouse models of psychosis.

Methods. In vitro assays were initially performed at the human and the mouse M4 mAChRs. The degree of allosteric effect, i.e. cooperativity, between VU0467154 and ACh were quantified in [3H]-N-methyl-scopolamine equilibrium binding, [35S]-GTPγS binding and ERK1/2 phosphorylation assays. In vivo assays assessed the ability of VU0467154 (1-10mg/kg) to reverse MK-801-induced locomotor hyperactivity (LMA) and disruption of pre-pulse inhibition (PPI).

Results. Binding and functional interaction assays revealed that VU0467154 displayed high binding and functional cooperativity with ACh at the mouse M4 mAChR. However, PAM effects were significantly smaller at the human M4 mAChR. Excitingly, VU0467154 reversed the MK-801 psychotic-like effects in both LMA and PPI.

Discussion. This study validates VU0467154 as a M4 PAM candidate that performed well in two drug-induced mouse models of psychosis, however also highlights high degree of species variability for the M4 mAChR. Further medicinal chemistry efforts around this M4 PAM may yield potential novel drug candidates for the treatment of Schizophrenia with improved efficacy for the human M4 mAChR.


Entry of valproate and lamotrigine into the developing brain

Samuel J Toll1, Norman R Saunders1, Mark D Habgood1, Katarzyna M Dziegielewskia1, Yifan Huang1, Fiona Qiu1. Dept of Pharmacol1, Univ of Melbourne, Parkville, VIC.

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

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

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

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

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

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

Tahlia R Meola1,2, Ahmad Y Abuhelwa1, Paul Joyce1,2, Peter Clifton1, and Clive A Prestidge1,2. UniSA: Clinical and Health Sciences, Adelaide, SA, Australia. ARC Centre of Excellence in Convergent Bio-Nano Science & Technology, Australia.

Introduction. Simvastatin (SIM) is clinically proven cholesterol-lowering drug which can reduce the risk of major cardiovascular events. However, SIM is poorly absorbed and undergoes extensive first-pass metabolism, resulting in a low oral bioavailability of less than 5%, after conversion to its active metabolite, simvastatin acid (SIMA)1. Silica-lipid hybrids (SLH) are a solid nanostructured lipid formulation proven to promote drug solubilisation, owing to a unique nanoporous matrix and high surface area2. Therefore, the current study aimed to reformulate SIM into a lipid formulation utilising SLH technology to enhance oral bioavailability.

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

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

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

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

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

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

Nicholas J Hunt 1,2,3,4, Glen P Lockwood 1,2, Sophie Kang 1,5, Lara J Westwood 6, Peter AG McCourt 3,7, Zdenka Kuncic 3,4,8, David G Le Couture 1,2,3, Victoria C Cogger 1,2, ANZAC Research Institute 1, Concord RG Hospital, Sydney, NSW, Australia. Faculty of Medicine and Health 2, Charles Perkins Centre 3, Sydney Nano Institute 4, School of Physics 8, The University of Sydney, Sydney, NSW, Australia. National Cancer Institute 5, National Institutes of Health, Bethesda, MD, United States. Faculty of Science 6, University of Technology Sydney, Sydney, NSW, Australia. Department of Medical Biology 7, University of Tromsø, Tromsø, Norway.

Orally administered Ag2S quantum dots (QDs) rapidly cross the small intestine and are taken up by the liver.1 Metformin and nicotinamide mononucleotide (NMN) target metabolic and aging processes within the liver. This study examined the pharmacology and toxicology of QD-based nanomedicines as carriers of metformin and NMN in young and old mice, determining if their therapeutic potency and reduced effects associated with aging could be improved.

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

Two weeks of treatment with low dose QD-NMN (0.8 mg/kg/day) improved glucose tolerance tests in young (3 month) mice while old (18-month, 24-month) mice demonstrated improved fasting and fed insulin levels and HOMA-IR. High dose unconjugated NMN (80 mg/kg/day) demonstrated improvements in young mice but not in the old mice. After 100 days of QD (320 µg/kg/day) treatment there was no evidence of cellular necrosis, fibrosis, inflammation, or accumulation of QDs. Ag2S QD-nanomedicines improved the pharmacokinetic and pharmacodynamic properties of metformin and NMN by increasing their therapeutic potency, bypassing classical cellular uptake pathways, and demonstrated efficacy when drug alone was ineffective in aging mice.

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

Jessica R. Tait, Phillip J. Bergen, Roger L. Nation, Cornelia B. Landersdorfer. Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia

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

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

Methods. A clinical isolate (MICTZP 4mg/L, MICTOB 0.5mg/L) from a critically-ill patient was evaluated in static concentration time-kill studies and subsequently studied in 120h dynamic in vitro infection models (IVM, inoculum 10⁶ CFU/mL, performed in n=2 replicates). The IVM simulated the PK of TZP (t₁/₂=1.5h) and TOB (t₁/₂=3.1h), based on published population PK models. Regimens were: A. TZP 4g q4h as 0.5h infusions; B. TZP 24g/day as continuous infusion (CI); C. TOB 7mg/kg q24h as 0.5h infusions; A+C; and B+C. Total viable counts were determined at 13 time points and resistant bacteria quantified at 24h intervals. Mechanism-based modelling was performed (lines in figure).

Results. In the IVM (Figure), A provided <4 log₁₀ CFU/mL initial killing, followed by regrowth close to control values by 72h. B provided 4.0-4.5 log₁₀ initial killing, followed by regrowth close to initial inoculum by 96h. C and A+C provided extensive killing (up to 6 log₁₀) after each TOB dose up to 54h, with regrowth to control values and starting inoculum, respectively, and resistance emergence by 72h. B+C provided extensive initial killing and suppression of regrowth (to <2 log₁₀) and resistance emergence over 120h.

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

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

Stephanie E Reuter, Hayley B Schultz, Michael B Ward, Crystal L Grant, Siobhan Banks and Allan M Evans

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

Aims. This study was conducted to examine the impact of caffeine consumption on the renal clearance of calcium (CaCLrenal), sodium (NaCLrenal) and creatinine (CrCLrenal) in healthy adults to provide mechanistic insight into the role of caffeine in calcium homeostasis.

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

Results. Mean CaCLrenal, NaCLrenal and urine output were 77%, 61% and 67% greater under caffeine conditions compared to placebo, respectively (p<0.05). In contrast, no significant difference between the treatments was seen for CrCLrenal (p>0.05). Statistically significant relationships between NaCLrenal and CaCLrenal (R²=0.47, p<0.0001) and NaCLrenal and urine output (R²=0.39, p<0.0001) were observed.

Discussion. For the first time, this study comprehensively examined the effect of caffeine on calcium economy and suggest that caffeine inhibits sodium reabsorption in the proximal convoluted tubule, thus increasing NaCLrenal, CaCLrenal and urine output. Considering the lack of impact of caffeine treatment on CrCLrenal, these findings were in contrast with the previously proposed effect of caffeine on glomerular filtration rate through vasoconstriction of the afferent arteriole. This preliminary study provides mechanistic insight into the role of caffeine in osteoporosis and fosters the further investigation into safe consumption of caffeine with a focus on bone health.
The effect of chronic polypharmacy and monotherapy on drug pharmacokinetics in mice.

John Mach1, XiaoSuo Wang2,3 & Sarah N Hilmer1.

Laboratory of Ageing and Pharmacology, Kolling Institute, Royal North Shore Hospital and Northern Clinical School, Faculty of Medicine of Health, University of Sydney, Sydney, NSW, Australia 1. Bosch Mass Spectrometry Facility, Bosch Institute, University of Sydney, Sydney, NSW, Australia 2. Freedman Foundation Metabolomics Facility, Victor Chang Cardiac Research Institute Innovation Centre, Sydney, NSW, Australia 3.

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

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

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

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

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


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

Aili Langford1, Danijela Gnjidic1, Chung-Wei Christine Lin2, Lisa Bero3, Fiona Blyth4, Jonathan Penm1, Carl R Schneider4. School of Pharmacy1, USYD, Sydney, NSW; Institute for Musculoskeletal Health2, USYD, Sydney, NSW; School of Medicine3, University of Colorado, Colorado, USA; School of Public Health4, USYD, Sydney, NSW.

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

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

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

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

Discussion. For opioid deprescribing guidelines to be effective, opioid consumers need to feel empowered to engage in opioid reduction. The findings of this study enable a patient-centred approach for practitioners and guideline developers in creating recommendations to facilitate opioid deprescribing through targeting behavioral change.
A meta-analysis on outcomes of medication misadventure among people with cognitive impairment or dementia

Anum S Zaidi1, Gregory M Peterson1,2, Luke RE Bereznicki1, Colin M Curtain1, Mohammed S Salahudeen1. School of Pharmacy and Pharmacol, Univ of Tasmania1, Hobart, TAS, Australia; Faculty of Health, Univ of Canberra2, ACT, Australia.

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

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

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

Results. The systematic review included 10 studies that reported the outcomes of mortality or hospitalisation associated with medication misadventure, including PIMs (n=5), ADEs (n=2), a combination of MEs and ADEs (n=2), and drug interactions (n=1). Five studies examining the association between PIMs and mortality/hospitalisation were included in the meta-analyses. Exposure to PIMs was not associated with either mortality (odds ratio [OR]=1.36; 95%CI=0.79-2.35) or hospitalisation (OR=1.02; 95%CI=0.83-1.26). In contrast, studies of cholinesterase inhibitors found that ADEs were associated with mortality and hospitalisation.

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

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

Mohammed B Ayalew1, 2, Gudrun Dieberg3, Frances Quirk1, Joy M. Spark1. Faculty of Medicine and Health, University of New England1, Armidale, NSW, Australia; Department of Clinical Pharmacy, University of Gondar2, Gondar, Amhara, Ethiopia; Biomedical Science, University of New England3, Armidale, NSW, Australia.

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

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

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

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

Discussion. IMPACT2DM is the first explicit tool specifically designed to identify PIP for adults with T2DM. The tool can be applied using information on medical charts and requires minimal or no clinical knowledge. IMPACT2DM can be used by researchers and clinicians to assess quality of diabetes care, improve medication selection, and educate health professionals who are working with diabetic patients.
Duration of postoperative opioid use after hip or knee surgery: a systematic review and meta-analysis

Hui Ping Tay¹, Xinyi Wang¹, Sujita W Narayan¹, Jonathan Penn¹, Asad E Patanwala¹,². School of Pharmacy, Faculty of Medicine and Health, the University of Sydney¹, Sydney, NSW, Australia; Royal Prince Alfred Hospital², Camperdown, NSW, Australia.

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

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

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

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

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

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

Natasha Taufatofua¹, Heena Akbar², Neil Cottrell¹,³ Adam La Caze¹. School of Pharm, Univ of QLD¹, Brisbane, Australia; Faculty of Health, QUT², Brisbane, QLD, Australia. Faculty of Health and Behav Sci, Univ of QLD³, Brisbane, Australia.

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

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

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

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

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

Understanding the imprecision of precision medicine

Sophie L Stocker1,2. Sydney Pharmacy School, Faculty of Medicine and Health, Sydney University1, NSW, Australia, Dept Clinical Pharmacology & Toxicology, St Vincent’s Hospital Sydney2, NSW, Australia.

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

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

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

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

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

Novel BRET approaches to understand the complexities of endogenous GPCR function

Carl W White. Harry Perkins Institute of Medical Research, Australia and Centre for Medical Research, The University of Western Australia, Nedlands, WA, Australia; Centre of Membrane and Protein and Receptors (COMPARE), Universities of Birmingham and Nottingham, UK.

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

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

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

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

Discussion. Using CRISPR/Cas9-mediated genome engineering, NanoBRET can be used to observe various aspects of receptor function using GPCRs found under endogenous promotion. This overcomes a major limitation of existing BRET-based techniques and helps to better understand the influence of cellular context on receptor function.
Rational design of dose individualisation strategies for 5-Fluorouracil (5-FU)

Stephanie E Reuter1. Quality Use of Medicines & Pharmacy Research Centre, UniSA Clinical & Health Sciences, University of South Australia1, Adelaide, SA, Australia.

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

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

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

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

Ashley M Hopkins1, Andrew Rowland1, Michael J Sorich1. College of Medicine and Public Health, Flinders University, Adelaide, Australia

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

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

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

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


Implementation and evaluation of a virtual pharmacy Objective Structured Clinical Examination (OSCE)

Vivienne Mak1, Sara Chuang1. Faculty of Pharmacy and Pharmaceutical Sciences, Monash University1, Parkville, VIC, Australia

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

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

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

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

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

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

Emily Reeve1-3, Marci Dearing1, Jennifer Isenor2, Kenneth Rockwood1,2, Kent Toombs1, Lisa Kouladjian-O’Donnell4, Sarah Hilmer5, Colin Van Zoot3, Heather Neville1, Caroline Sirois5, Olga Kits1,2, Mohammad Hajizadeh2, Susan Bowles1,2. Nova Scotia Health Auth1, NS, Canada; Dalhousie Univ2, NS, Canada; Clin Health Sci, Univ of South Aus3, Adelaide, SA; Kolling Inst, Royal North Shore Hosp and Sydney Univ4, St Leonards, NSW; Fac Med, Laval University5, QC, Canada.

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

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

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

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

Discussion. The intervention may be effective at reducing DBI scores in older adults during hospitalisation, however, significant feasibility issues were identified. Further work is required to determine the best way to integrate The DBI Calculator© into pharmacist workflow in hospital.
306
Understanding the mechanisms behind the oral bioavailability enhancement of abiraterone acetate by silica-lipid hybrid formulations

Hayley B Schultz1, Paul Joyce1, Anthony Wignall1, Nicky Thomas1, Clive A Prestidge1.
UniSA Clinical & Health Sciences, University of South Australia1, Adelaide, SA, Australia.

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

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

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

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

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


307
Evaluation of a pilot vancomycin therapeutic drug monitoring (TDM) service using an interrupted time series analysis

Jane E Carland1-2*, Sophie L Stocker1-2*, Stephanie E Reuter3, Alexandra E Stacy1,4, Andrea L Schaffer5, Maurizio Stefani1, Cindy Lau6,7, Ranita Kirubakaran1-2, Jennifer Yang1,2, Catriona FJ Shen1,2, Darren M Roberts1,2, Deborah JE Marriott2,8, Ranita Kirubakaran1,2, Jennifer Yang1,2, Catriona FJ Shen1,2, Darren M Roberts1,2, Deborah JE Marriott2,8, Richard O Day1,2, Jonathan Brett1,2, Clin. Pharm & Toxicol, St Vincent’s Hospital, Sydney, NSW1; St Vincent’s Clinical School, UNSW Sydney, NSW2; UniSA Clinical & Health Sciences, University of South Australia, Adelaide, SA3; School of Medicine, Notre Dame University, Sydney, NSW4; Centre for Big Data Research in Health, Faculty of Medicine, UNSW, Sydney5; Pharmacy Dept, St Vincent’s Hospital, Sydney, NSW6; School of Pharmacy, Faculty of Medicine & Health, The University of Sydney, Sydney7; Clin. Micro. & Infectious Diseases, St Vincent’s Hospital, Sydney8

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

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

Methods. A retrospective audit of intravenous vancomycin therapy (>48 hours) in adults (≥18 years) was undertaken over a 54-month period to evaluate attainment of established vancomycin pharmacokinetic/pharmacodynamic targets (AUC24/MIC 400-600) pre- (36-months) and post- (18-months) implementation. Interrupted time series analysis was employed to evaluate monthly measures of the median proportion of therapy spent within the target range. Indices of time to target attainment were also assessed pre- and post-Service implementation.

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

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

*Authors contributed equally to the work.
Supporting and including our International students

Betty Exintaris, Nilushi Karunaratne and Suzanne Caliph. Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia.

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

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

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

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

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

Promoting gender equity and diversity in the classroom

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

What does it mean to promote gender equity and diversity in our classrooms? In this presentation I take a design approach to inclusion in our education, using a model for analysis of complex learning environments that considers physical and virtual design, task design and design for social interaction. These three design aspects converge to create the student experience and the learning behaviours that emerge from participation. Further, the language we use, the ways in which we encourage participation and how we reinforce our learners in real time are critical to a student’s sense of belonging. I will demonstrate with examples and an historical analysis of curriculum components what we can all do to design for and promote equity and diversity in our classrooms.
310

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

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

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

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

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

311

Strengthening Indigenous health workforces

Adams, K. Gukwonderuk Indigenous Health Unit, Monash University, Clayton, VIC, Australia.

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

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

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

Discussion. Over the three years there was a pattern of improved student reaction and learning. The online delivery was scalable, overcame a barrier of educator skill and confidence to teach this area and provided critical consciousness building with students self-reflecting and planning how to act. In contrast, if teaching had occurred in small group oral discussions it would have been more difficult to ascertain teaching and learning occurring and undoubtedly students would have received different messaging based on individual educator skill and confidence. Interestingly, learning gained from this unit matched that described as occurring from student placements in health settings with high numbers of Indigenous people. The discrete unit rapidly increased the level of Framework teaching and assessment in this undergraduate degree, higher than the average for Faculty disciplines attempting to integrate Indigenous health content. Notably the self-rated survey showed change for 23 items compared to five for a first-year integrated curriculum. Connecting this research to Faculty level committee led to widening success across the Faculty and improved sustainability of the practice. Equity in admissions of Indigenous students improved over the five-year period despite significant systematic challenges and obstacles.
Dysregulated ALX/FPR2 ligand expression defines a novel molecular subtype of lung cancer

Steven Bozinovski. School of Health & Biomedical Sciences, RMIT University, Bundoora, VICTORIA, Australia.

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

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

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

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

Lipoxins, a novel approach to treat diabetes-associated atherosclerosis

EP Brennan1, M. Mohan2, M.de Gaetano1, M. Barry3,P. Guiry4 K Jandeleit-Dahm2, M. Cooper2, P. Kantharidis2 Catherine Godson1

1Diabetes Complications Research Centre, Conway Institute & School of Medicine, 3St Vincent’s University Hospital, & 4Centre for Synthesis and Chemical Biology, University College Dublin, Ireland. 2Department of Diabetes, Central Clinical School, Monash University, Clayton, Vic, Australia.

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

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

The financial support of Science Foundation Ireland, Health Research Board Ireland, Irish Research Council a JDRF Strategic Research Award and AHMRC is gratefully acknowledged
Advances in specialized pro-resolving mediator (SPM) G protein-coupled receptors
Jon Merlin1, Julia Park1, Christopher J Langmead1 and Darren M Riddy1.
Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University1, VIC, Australia;
Resolution of inflammation is regulated by specialised pro-resolving mediators (SPMs, such as resolvins and lipoxins) and their
proposed cognate G protein-coupled receptors (GPCRs), including FPR2, BLT1, chemerin1, GPR32, GPR18 and GPR37. These
receptors coordinate activity of peripheral blood mononuclear cells (PBMCs) and polymorphonuclear leukocytes (PMNs).
However, the comparative pharmacology of SPMs and native immune cell expression profile of SPM-GPCRs are not well
understood.
Therefore, we profiled (a) the expression levels of these SPM-GPCRs in PBMCs and PMNs of healthy human blood, and (ii)
their responses to SPMs and surrogate ligands when stably expressed in HEK293 cells. Human CD14+ PBMCs and CD66b+ PMNs
were isolated from whole blood utilising magnetic separation. FACS revealed almost ubiquitous expression of BLT1 and GPR32
on the surface of PBMCs (89.5 ± 5.9% and 88.0 ± 7.7%; n=6-12) and PMNs (98.9 ± 0.9% and 87.5 ± 8.0%; n=6-11). FPR2 and
chemerin1 had a more restricted expression profile on PBMCs (29.3 ± 14.0% and 31.3 ± 18.7%; n=11-12) and PMNs (25.8 ±
14.8% and 14.5 ± 12.4%; n=11-12), whilst GPR18 was more abundantly expressed on PMNs (92.8 ± 3.3 %; n=6) versus PBMCs
(34.3 ± 25.4%; n=6). No expression of GPR37 was detected.
However, with the notable exception of resolvin-E1 at BLT1, none of the previously reported SPM – SPM-GPCR ligand pairings
were reproduced in multiple G protein-dependent or independent signalling assays in HEK293 cells in which canonical and
synthetic ligands were robustly active (e.g. leukotriene-B4-stimulated BLT1 activation, WKYMVm-stimulated FPR2 activation).
These data suggest that there may be more complex mechanisms by which SPMs interact with SPM-GPCRs in their native
environment, if at all. Further studies in PMNs and PBMCs will be required to establish native SPM-GPCR pharmacology.

Cardioprotective potential of resolving inflammation in the heart
Rebecca H Ritchie. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC
Australia 3052.
Inflammatory disorders such as diabetes and myocardial infarction are major causes of heart failure, which remains a key
cause of death across the globe. The annexin-A1 (ANX-A1)/formyl peptide receptor (FPR) axis is integral to inflammation and
its resolution. This presentation explores the potential for targeting this ANX-A1/FPR axis for cardioprotection, beyond their
early anti-inflammatory effects to the prevention of late cardiac remodelling and dysfunction after myocardial inflammatory
insults in mice in vivo. Choice of FPR ligand is key to the cardioprotective potential in the context of inflammatory disorders,
whether small-molecule or peptide/lipid mediator based, and whether the ligand exhibits FPR-subtype selectivity and/or
biased signalling downstream of FPR activation. Therapeutic targeting the ANX-A1/FPR axis may represent one approach to
enhance the resolution of inflammation, and hence delay progression to heart failure, in both diabetic and ischaemic cardiomyopathies.
316

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

Janet K Sluggett1,2,3. UniSA Allied Health and Human Performance, University of South Australia1, Adelaide, SA, Australia; Registry of Senior Australians, South Australian Health and Medical Research Institute2, Adelaide, SA, Australia; Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University3, Parkville, VIC, Australia.

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

317

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

Mouna J Sawan1. Syd Pharm School, Faculty of Med and Health1, Univ of Sydney, NSW, Australia

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

J Simon Bell1, Leonie Picton2. Centre for Medicine Use and Safety, Monash University1, Melbourne, VIC, Australia

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

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

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

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

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


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

Gillian E Caughey1,2, Maria C Inacio1,2, Catherine Lang1,2, Sarah Bray1,2, Stephanie Harrison1, Craig Whitehead1, Renuka Visvanathan1, Keith Evans1, Megan Corlis1, Victoria Cornell1, Steve Wesselingh1 Registry of Senior Australians (ROSA), SAHMRI1; UniSA Allied Health and Human Performance, University of South Australia2, Adelaide, SA, Australia.

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

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

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

Results. Of the 5 indicators estimated nationally; antibiotic use (67.5%, 95% CI 67.3-67.7%) had the highest prevalence, followed by high sedative load (48.1%, 95%CI 47.9-48.3%), chronic opioid use (26.8%, 95%CI 26.6-26.9%), antipsychotic use (23.5%, 95%CI 23.4-23.7%). Of the 7 indicators estimated in SA ED presentations (19.1%, 95%CI 18.3-20.0%) had the highest prevalence, followed by hospitalisation for falls (10.1%, 95%CI 9.7-10.4).

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