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An Evaluation of Switches in Therapeutic Equivalents as Triggers for Adverse Event Monitoring

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Introduction: General Practice electronic clinical records contain data that could be used to identify adverse events. Trigger tools could be developed to help identify when adverse events have occurred.
Objective: To examine changes in a therapeutic equivalent (antidepressant) in relation to reports of adverse drug events (ADEs) and symptoms indicative of ADEs within general practice electronic records.
Methods: Electronic clinical records for a cohort of 338,931 patients consulting from 2002-2007 were extracted from the patient management systems of 30 primary care clinics in New Zealand. A structured chronological analysis of prescriptions, consultation notes and adverse events relating to patients prescribed the SSRI citalopram was undertaken included investigating reasons for switching treatment to another SSRI (fluoxetine or paroxetine) as a method for detecting evidence of ADEs.
Results: During the study period 173,478 patients received 4,811,561 prescriptions. Citalopram was prescribed for 5,612 patients and 610 adverse reactions to citalopram were identified in the consultation and medical warning records of 397 (7.1%) patients. A total of 713 (12.7%) patients changed treatment from citalopram to another SSRI. Reasons for switching were identified for 164 patients: ADE for 129 (78.7%), lack of effect for 29 (17.7%) and patient preference for six (3.7%). The most common ADEs preceding the switch were anxiety, nausea and headaches.
Conclusions: A switching of therapeutic equivalent can be used as a trigger for reports of ADEs.

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Measuring drug concentrations, analytical methods and issues

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Introduction. The primary goal of Therapeutic Drug Monitoring (TDM) is to improve patient outcomes. In order to support this goal, the analytical approach underpinning TDM must be robust and reproducible, requiring validation to a standard suitable for regulatory approval.
Discussion. TDM is most commonly used for small drug molecules and their metabolites measured in plasma/serum or whole blood. However many other matrices are used and increasingly large molecule "biological" drugs are being used in clinical practice. There are a number of analytical techniques that can be used to measure drug concentrations and these will be the focus of this presentation. These techniques typically involve first separating the compound of interest form its biological matrix (plasma, whole blood or urine); this may be achieved through high (or ultra) performance liquid (or gas) chromatography (HPLC / UPLC / GC). Once the compound of interest has been isolated, it is then quantified either by measurement of ultra-violet absorbance, fluorescence or by mass spectrometry. When developing and validating an analytical method for use in TDM there are several key factors that must be consider. These are: accuracy (bias and imprecision), specificity, limit of detection, limit of quantitation/identification, linear dynamic range, reproducibility, repeatability, robustness and timeliness. Selection of an analytical approach for undertaking TDM must therefore be based on fitness for purpose and the capacity of the technique to address these factors in a manner appropriate to the drug being measured and does not necessarily require the use of the most sophisticated or modern technology.

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New Zealand Formulary - a case study of national formulary development

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Introduction. The New Zealand Formulary (NZF) was developed to build on the New Zealand Universal List of Medicines through the addition of clinical information about medicines use. The structure and content of the NZF is based on that of the British National Formulary (BNF) but is adapted for New Zealand practice. It contains key information on the selection, prescribing, dispensing, and administration of medicines available as an online resource.
Aim. To adapt the BNF to provide New Zealand (NZ) healthcare professionals with information about the selection, prescribing, dispensing, and administration of medicines by July 2012.
Methods. The initial release of the NZF was adapted from the latest version of the BNF focusing on relevance to NZ practice. The BNF therapeutic notes were reviewed by medical specialist advisors and clinical pharmacists before they were ?signed-off? by an editorial advisory board. The BNF monographs were compared to NZ approved Medicine Datasheets (NZAMD) and tailored to reflect NZ approved indications and doses. Other fields of the monographs were also reviewed and additional detail and practical advice was added where appropriate including inclusion of Stockley' s interaction alerts and Australian eTG breast-feeding categories. Where advice differed from the NZAMD, careful validation was undertaken using alternative sources of information and expert advisors as necessary.
Results. The NZF was successfully developed within the specified contract timeframe and budget. It was also being utilised by the health sector with 57,809 visitors in the first 3 months. Also, in the first 3 months the average number of daily users has consistently increased to 713. Clinical feedback is divided into domains that are evaluated for future enhancements.
Discussion. The BNF can be successfully adapted in a timely and cost effective manner to the NZ context.

Joint Formulary Committee (2012) British National Formulary, 63ed London, BMJ Group and Pharmaceutical Press

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Evaluation of formulary applications in Australian paediatric hospitals

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Introduction. Evaluation and approval of drugs for use in hospitals is a primary objective of hospital drug and therapeutics committees. Despite international legislative and regulatory changes, the evidence base informing care for children remains poor, compared with adults. There is limited information in the published literature regarding the evaluation of drug approval processes in paediatric hospitals.
Aims.1. To evaluate the quality of applications for addition to the formulary in Australian paediatric hospitals2. To evaluate the data supporting paediatric formulary applications including committee decisions3. To identify gaps in research relating to use of drugs in children and policy implications
Methods. Multicentre descriptive study involving review of committee documents and drug submissions for all Australian paediatric hospital Drug and Therapeutics Committees over an 18 month period. Main outcome measures: application format, type of supporting literature, committee decision, declaration of conflict of interest.
Results.All eight paediatric hospitals agreed to take part. The total number of formulary applications was 121. Approval rates varied from 58-100% for each hospital. To date, we have analysed 88 (73%) applications and found that most applications (68%) were formally submitted using a standardised templateby medical staff (65%).39% of applications underwent independent review by a statewide medicines advisory committee or hospital pharmacist. A conflict of interest was declared for 9(10%) applications. Quality of supporting data varied with many applicants including the product information, therapeutic guidelines and review papers as the predominant literature.
Discussion. These data confirm previously reported high approval rates for paediatric formulary submissions (Sinha YK et al 2010). Our preliminary findings suggest there is limited high quality evidence informing hospital-based drug approvals. This study provides a new national dataset relating to therapeutic decision making in tertiary paediatric hospitals.

Sinha YK et al (2010) Arch Dis Childhood 95:739-744

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Diagnostic errors in older patients: A systematic review of the incidence and causes in thirteen prevalent conditions.

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Background: Misdiagnosis, either over or under-diagnosis, exposes older patients to increased risk of inappropriate or omitted investigations and treatments, psychological distress and financial burden.
Objectives: To evaluate the frequency and causal factors of diagnostic errors relating to thirteen conditions prevalent in older patients.
Data sources and study selection: Cohort studies, cross-sectional studies or systematic reviews of such studies published in Medline between January 2001 and July 2011 were searched using key search terms of "diagnostic error" "misdiagnosis" "accuracy" "validity" or "diagnosis" and terms for each disease.
Data synthesis: Of 1260 retrieved articles, 29 were selected for inclusion. Rates of over-diagnosis and under-diagnosis were as high as 69% and 71% respectively with some conditions both under- and over-diagnosed. Over-diagnosis rates of more than 10% were seen in chronic obstructive pulmonary disease (18% - 35%), stroke and transient ischaemic attack (11% - 71%), major depression (22% - 69%), Parkinson's disease (1% - 27%), heart failure (1% - 64%) and epilepsy (16%). Under-diagnosis rates of more than 10% were seen in ischemic heart disease (2% - 34%), major depression (12% - 53%), Parkinson's disease (9% - 47%), heart failure (4% - 71%) and epilepsy (16% - 27%).
Conclusion: Diagnostic errors involving older patients are common and comprise both over-diagnosis and under-diagnosis. Explanations for over-diagnosis include the subjective interpretation of clinical diagnostic criteria and use of criteria which have not been validated in older patients. Under-diagnosis was associated with long pre-clinical phases of disease or lack of sensitive diagnostic criteria. Factors that predispose to misdiagnosis in older patients must be given emphasis in training programs and clinical practice guidelines.

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An evaluation of a change in dosing regimen of gentamicin in neonates

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Introduction. It has previously been demonstrated that clinically significant variability and delay in the administration of gentamicin occurs in neonates and is related to the method of administration.[1]
Aim. To compare the effects of two dosing methods on the delivery of gentamicin to neonates.
Methods. Two dosing methods were compared; bolus and a 30 minute infusion. Neonates admitted to Dunedin Neonatal Intensive Care Unit (NICU), in 2008 and 2010 that had a gentamicin dose in the first three days of life and a one hour peak and 23 hour trough level, were included in the study. A pharmacokinetic (PK) analysis was performed with Phoenix NLME using a zero order input and first order elimination. Duration (Tinf1=2010, Tinf2=2008) of infusion was parameterised separately for each dosing method. The model was optimised using a covariate approach.
Results. There were 73 patients in 2010, 31 females and 42 males; and 97 patients in 2008, 36 females and 61 males. The median and range values were: 2010; gestational age (GA) 37.714weeks (24.286-41.857) and weight (W) 3.165kg (0.51-5.65), 2008; GA 34.643weeks (23.429-42) and W 2.413kg (0.49-5.105). The parameter estimates were: V = 1.205 * (W/mean(W))^0.835 * exp(nV)); Cl = 0.097 * (W/mean(W))^0.9015 * (GA/mean(GA))^1.233 * exp(nCl)); Tinf1 = 1.05; Tinf2 = 0.901. The magnitude of inter-patient variability, expressed as CV% were <20%. The magnitudes of residual error in the dosing methods were, 0.414 for Tinf1 and 0.469 for Tinf2.
Discussion. There was no significant difference in the duration of the infusion between the two years. This suggests further PK analysis is required on the input of gentamicin in neonates.

[1]Sherwin C. et al. (2009) JPP 61:465-461

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Anti-arthritic and anti-proteus activities of colloidal metallic silver (CMS)

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Introduction. Colloidal silver has been used as an antibiotic for over 100 years (Cock et al 2012). Patients with rheumatoid arthritis may produce antibodies to both *Proteus* bacteria and to proteins containing citrullinyl residues. *Proteus* are enterobacteria also found in the upper urinary tract (notably in females), that can transform protein-arginyl residues to antigenic protein-citrullinyl residues.
Aims: To investigate antibiotic efficacy of CMS against an arthritigenic bacterium.
Methods. Anti-arthritic activity was evaluated after orally administering colloidal metallic silver (CMS) to female Wistar rats developing chronic polyarthritis after tailbase injection of either (i) a complete Freund's adjuvant or (ii) collagen type-II with an incomplete Freund's adjuvant or (iii) pristane. Anti-proteus activity was determined by a disc diffusion assay growing *P.vulgaris* and *P.mirabilis* on agar plates in the presence of various CMS preparations.
Results. A. CMS preparations made electrolytically and administered orally (alternate days for two weeks) were powerful anti-arthritic agents in rats (ED_{80} approx. 85 µg/kg total silver). Monovalent silver products (acetate, nitrate, oxide) were ineffective at twice this dose.
B. CMS preparations were also more potent than silver salts in suppressing growth of *Proteus* sp. *in vitro*. Against *P.mirabilis,* minimal inhibitory concentrations (MIC) of total silver were greater than 22µg/ml for chemically prepared CMS and less than 3 g/ml for electrolytically prepared CMS: the difference being due to the smaller size of nanoparticles and different Zeta potentials in electrolytic preparations, compared with chemical preparations, of CMS.
Discussion. Pro-arthritic gut micro-organisms may be susceptible to 'old' antibiotics taken orally such as colloidal silver, as well as to accepted slow-acting anti-rheumatic drugs (DMARDs) originally developed as antibiotics eg minocycline, salazopyrine. More rigorous Quality Controls must be developed for the preparation of CMS – as well as antimicrobial efficacies and general safety.

Cock I et al (2012) Pharmacognosy Communications; 2:47-56.

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Monitoring the Anti-Proteus activity of Colloidal Metallic Silver (CMS) *in vivo* using the Metatron/Hunter.

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Introduction. Rheumatoid arthritis (RA) may be initiated/sustained by certain infections notably *Proteus sp*. found in soil, water and the human gut (Ebringer & Rahsid 2006) and *Porphyromonas gingivalis* within diseased gums of the mouth(Loyola-Rodrigeuz et al 2010). In rats, certain preparations of colloidal metallic silver (CMS) are anti-arthritic and also effective antibiotics against *Proteus sp. ex vivo* (Whitehouse & Cock 2012).
Aims. (=proof of concept): To test whether pre-selected nanoparticulate CMS hydrosols might be effective antibiotics against *Proteus in vivo*.
Methods. A male volunteer without overt arthritis was identified as carrying *Proteus sp*. in the large bowel and urinary bladder. The degree of infection was monitored non-invasively with a MetAtron/Hunter^{R} (IPP, Omsk) before and after oral ingestion of a CMS preparation, LunAsol^{R} (LR-049) at a dose of 200 micrograms Ag bid for 8 days. [The MetAtron is a non-linear scanning device which can locate and semi-quantify *Proteus* by its unique bioresonance frequency (Sylver 2009) in a total body scan.]
Results. A relatively low dose of silver (total = 3 mg; 40µg/kg) reduced the *Proteus* burden by 90%, 86% and 86% respectively in the large bowel, the bladder and the urethra. This response was sustained for over four weeks after ceasing CMS dosing. No toxic symptoms accompanied this treatment.
Discussion. This diagnostic instrument can physically sense some potentially arthritigenic microbial populations *in vivo*. The MetAtron appears suitable for wider therapeutic applications, particularly a) selecting patients for study; b) finding optimal doses of antibiotics and c) helping correlate clinical responses with antimicrobial activities.

Ebringer A, Rashid T (2006) Clin Develop Immunol 13:41-48.
Loyola-Rodrigeuz JP, et al 2010 J Oral Microbiol, Dec 21;2. doi: 10.3402/jom.v2i0.5784.
Sylver N (2009) Handbook of Frequency Therapy. Phoenix Az. Desert Gate. 732 pp.
Whitehouse M, Cock I (2012) Int Med J Abstr Suppl (May)10

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Posterior, subcapsular cataract in association with fludrocortisone acetate therapy: a case report

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Introduction. The product information (PI) of fludrocortisone acetate (FA) contains a class warning about cataract formation during use. However, there are no case reports of FA associated cataract in the literature. We report the first case of a posterior, subcapsular cataract (PSC) in association with high-dose FA used for postural hypotension secondary to antidepressant therapy.
Case Report. A 59-year-old, male, Caucasian physician with treatment resistant major depression was taking phenelzine 45 mg daily, complicated by severe postural hypotension; supine BP 120/70 mmHg, standing 60/30 mmHg. Minor exercise resulted in claudication, loss of colour vision and interscapular chest pain, which resolved with recumbency. Neither salt nor fluid loading alleviated the symptoms. Symptoms resolved on FA at 0.2 mg b.d. with supine BP 150/100 mmHg, standing 120/80 mmHg. After four months the patient noticed loss of acuity and a 'blue haze' in his right eye. Acuity was 6/36 and examination revealed a large PSC. Lens extraction and insertion of an intra-ocular lens was performed.
Discussion. FA (Florinef®) is a halogenated derivative of hydrocortisone. It has a mineralocorticoid potency > 100-fold that of hydrocortisone but is also 10–15 times more potent as a glucocorticoid. FA promotes sodium resorption at the distal tubule with a resultant increase in plasma volume leading to its use in postural hypotension The Australian PI for FA states that "Prolonged use of corticosteroids may produce posterior subcapsular cataracts". Similar statements are made for products in the UK and USA. However, a literature search including Medline®, Embase®, and the Database of Adverse Event Notifications, Australia; MedEffect® Canada; MedWatch, USA; and Drug Analysis Prints, UK found no cases of any form of cataract in association with FA.
Conclusion. This case demonstrates that when fludrocortisone acetate is used in higher doses adverse effects associated with its glucocorticoid activity may occur.

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Evaluating posaconazole use in a patient population.

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Introduction. Posaconazole is approved for prophylactic use against invasive fungal infections (IFIs) and treatment of refractory infections. It exhibits highly erratic absorption partly due to its high lipophilicity. Oral availability is reduced by proton pump inhibitors (PPIs) and pro-gastric motility agents. Absorption is increased by concomitant food intake and by dividing the daily dosage. Therapeutic dosage monitoring (TDM) is recommended to maintain plasma concentrations above a putative target of 700 ng/ml.
Aims. (1) To determine if adequate plasma concentrations are achieved in patients at risk (prophylaxis) or being treated for fungal infection and, (2) identify any drug-drug interactions or clinical factors which alter concentrations.
Methods. An audit of patients prescribed posaconazole at the study site was undertaken for the period June 2007 to June 2012. TDM data and patient records were reviewed. Concentrations were excluded if records indicated missed dose prior to sampling. Proven or probable IFIs were identified in the prophylactic cohort. Data are presented as median and 95% CI.
Results. Seventy-eight patients were prescribed posaconazole. From 68 patients, 511 plasma concentrations were available. Median concentrations were <700 ng/ml in 48 patients, 6 of these patients continued with posaconazole despite low concentrations and ongoing neutropenia. Low concentrations were observed with concomitant PPI usage (369 [209-542] ng/ml vs. 620 [346-1183] ng/ml, $p<0.0001$, with and without PPI, respectively; n= 34 patients). In-patient concentrations were significantly lower than out-patient (470.5 [298-731] ng/ml vs. 1021 [419-1587] ng/ml, $p<0.0001$) .Six of 62 patients prescribed posaconazole for prophylaxis failed therapy, the median of their concentrations were similar, though lower, than for patients who did not have a fungal breakthrough (446 [265-808] ng/ml vs. 531 [327-1042] ng/ml, $p=0.18$).
Discussion. Sub-therapeutic levels of posaconazole were common. Concomitant PPI usage and in-patient status were associated with sub-therapeutic concentrations. Guidelines involving TDM are needed to improve posaconazole's use.

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Electronic prescribing in St Vincent's hospital and the National Inpatient Medication Chart audit

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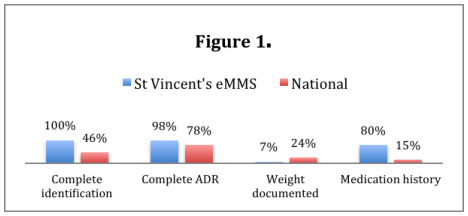
Introduction. The National Inpatient Medication Chart (NIMC) Audit System assists Australian hospitals auditing their use of the NIMC. The nationally coordinated NIMC audit occurs every two years. In 2005, St Vincent's Hospital(SVH) introduced an electronic medication management system (eMMS) and now every ward of the hospital is using the eMMS.

Aims. To compare St Vincent's Hospital, Sydney NIMC Audit data with the national data and identify areas of good medication management practice and how these relate to an electronic Medication Management System.

Methods: On August 28th 2012 we audited 141 patient medication charts in SVH using the NIMC audit form. We used the Australian Commission on Safety and Quality in Health Care NIMC audit website to generate Excel reports of the national and local results of the NIMC audit.

Results. 9689 patient medication charts in 312 hospitals were audited. In St Vincent's Hospital 121 electronic charts from inpatient wards and 20 paper charts from the emergency department were audited. Figure 1 identifies a number of differences between medication chart documentation in SVH and the national data. 50% of patients in SVH were prescribed VTE Prophylaxis compared with 19% nationally. Some parameters are not applicable to the electronic medication management system and were not recorded.



Discussion. A forcing function in eMMS of Adverse Drug reactions has resulted in better documentation in St Vincent's Hospital and this could be applied to other parameters. Pharmacy Annotation was markedly better on electronic charts. Documentation of weight and indication could be improved at SVH.

Coombes ID et al (2011)Br J Clin Pharmacol 72(2):338-49

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Kavalactones: Novel positive modulators of $\alpha_1\beta_{2/3}\gamma2L$ $GABA_A$ receptors

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Introduction. Kava (Piper methysticum) extract has gained popularity as intoxicating beverage due to its anxiolytic and sedative effects. Previous studies indicate that kavalactones affect a variety of molecular targets including the inhibitory ionotropic $GABA_A$ receptors. (Rowe A et al, 2011)

Aims. Characterizing kavalactones on $GABA_A$ receptors.

Methods. The effect of kavalactones (kavain, yangonin, methysticin and dihydromethysticin) was evaluated on recombinant $\alpha_1\beta_x\gamma_{2L}$ (x=1-3) $GABA_A$ receptors expressed in Xenopus oocytes using two electrode voltage clamp.

Results. The kavalactones (100 μM) had no effect alone or as modulators of GABA on $\alpha_1\beta_1$ and $\alpha_1\beta_1\gamma_{2L}$ but enhanced the action of GABA (EC_{10}) at $\alpha_1\beta_2\gamma_{2L}$ by 65-80%. The EC_{50} of kavain was not significant differently (P>0.05, t-test) between $\alpha_1\beta_{2/3}\gamma_{2L}$ ($EC_{50}(\alpha_1\beta_2\gamma_{2L})$ = 44.23 [95%CI 22.24–87.96, n=7]μM; $EC_{50}(\alpha_1\beta_3\gamma_{2L})$ = 63.23 [95%CI 49.05–81.51, n=3]μM) and $\alpha_1\beta_{2/3}$ ($EC_{50}(\alpha_1\beta_2)$ = 29.67 [95%CI 11.17–78.78, n=8]μM; $EC_{50}(\alpha_1\beta_3)$ = 60.11 [95%CI 36.62–98.66, n=8]μM). Flumazenil (0.1-10 μM) did not block the potentiation of GABA by kavain on $\alpha_1\beta_2\gamma_{2L}$. The efficacy ($E_{MAX}$) of kavain/yangonin was reduced 2-3 fold at $\alpha_1\beta_{2N265S}\gamma_{2L}$ (E_{MAX}(kavain) 44.80 [95%CI 33.36–56.25, n=5]%; E_{MAX}(yangonin) 28.77 [95%CI 18.22–39.31, n=4]%) and $\alpha_{1M236W}\beta_2\gamma_{2L}$ (E_{MAX}(kavain) 40.05 [95%CI 29.56–50.53, n=6]%; E_{MAX}(yangonin) 26.37 [95%CI 15.81–36.92, n= 5]%), relative to wild-type. However, the EC_{50} of kavain/yangonin was not significant differently from the wild-type at both $\alpha_1\beta_{2N265S}\gamma_{2L}$ (EC_{50}(kavain) = 37.34 [95%CI 24.08–57.90, n=5]μM; EC_{50}(yangonin) = 49.55 [95%CI 16.43–231.6, n=4]µM) and $\alpha_{1M236W}\beta_2\gamma_{2L}$ (EC_{50}(kavain) = 32.49 [95%CI 19.19–55.01, n=6]μM; EC_{50}(yangonin) = 5.830 [95%CI 1.251–27.17, n= 5]μM).

Discussion. Kavalactones are not binding to the benzodiazepine site but act as positive modulators of $GABA_A$ receptors containing β_2/β_3, while not affecting β_1. β_{2N265} and α_{1M236} may be involved in either receptor gating and/or binding of kavalactones.

Rowe A et al (2011). Kavalactone pharmacophores for major cellular drug targets. Mini reviews in medicinal chemistry 11(1):79-83

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Rat model of varicella zoster virus (VZV) induced neuropathic pain

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Introduction. Pain that persists for greater than 3 months after the shingles rash has healed is known as postherpetic neuralgia (PHN), a condition notoriously difficult to treat. Hence, there is a large unmet medical need for new treatments to alleviate PHN.
Aim. To establish a rat model of VZV-induced neuropathic pain for assessing the analgesic efficacy of novel molecules for neuropathic pain relief.
Methods. The Ellen strain of VZV was propagated *in vitro* in cultured MRC-5 cells to ~80% confluence. VZV infection of MRC-5 cells was confirmed by RT-PCR and Western blot using an antibody against the VZVgE protein. Adult male Wistar rats were randomized to one of three groups (n=4-6 per group) that received unilateral intraplantar injections (50 μL) of: (i) Phosphate buffered saline (pH7.4, 1mM, control group), (ii) MRC-5 cells ($7x10^6$ cells/ml; sham group) or (iii) VZV-infected MRC-5 cells containing 10^4 plaque forming units. Von Frey filaments were used to define the time course for the development of mechanical allodynia in the hindpaws and to assess the analgesic effects of single bolus subcutaneous doses of gabapentin at 10, 30 & 60mg/kg. A dose-response curve was generated and the ED_{50} was estimated using nonlinear regression (GraphPad Prism™ v5.03).
Results. VZV infection of MRC-5-cells was confirmed by RT-PCR and Western blot. Bilateral mechanical allodynia was fully developed in the hindpaws of VZV-injected animals (paw withdrawal thresholds ≤ 6g) by day 7 and maintained until at least day 35. Gabapentin produced dose-dependent relief of hindpaw hypersensitivity and the mean ED_{50} was 25.0mg/kg.
Discussion. A VZV-induced rat model of neuropathic pain has been established.

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Balb/c, C57BL/6J and CBA mice: characterisation of a new population of MDMA (ecstasy) users

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Introduction. MDMA-induced hyperthermia is the major feature in acute toxicity cases and is known to potentiate the neurotoxic effects of MDMA. Although there is a well documented role for 5-HT and dopamine (Mechan et al, 2002), microglial activation has recently been implicated in potentiating MDMA-induced hyperthermia (Orio et al, 2004). We propose to exploit inherent differences in mouse strains to further explore the involvement of microglia activation in MDMA-induced hyperthermia.
Aims. To develop a novel model in three mouse strains to investigate the mechanisms behind MDMA-induced hyperthermia.
Methods. Male Balb/c, C57BL/6J and CBA mice were administered MDMA (20 and 40 mg/kg, i.p) and body temperature and locomotor activity were monitored for 4 h at an ambient temperature of 22-23.5 °C.
Results. MDMA administered in Balb/c mice was shown to decrease body temperature significantly compared to saline (n=7-8, $P<0.01$), with 20 mg/kg MDMA seen to decrease body temperature more rapidly than 40 mg/kg MDMA. When given in C57BL/6J mice, MDMA increased body temperature significantly compared to saline (n=8-10, $P<0.001$), however there was no significant difference between 20 and 40 mg/kg MDMA. MDMA given in CBA mice produced a significant dose dependent increase in core body temperature (n=4-10, $P<0.001$). MDMA was seen to significantly increase locomotor activity in all strains at a dose of 40 mg/kg when compared to saline controls (n=4-10, $P<0.05$), however at a dose of 20 mg/kg, only C57BL/6J and CBA mice showed significantly increased locomotor activity (n=4-10, $P<0.05$).
Discussion. These results clearly display heterogeneity of response to MDMA in three mouse strains, with respect to both body temperature and locomotor activity. The results validate the model by providing a foundation on which to investigate the underlying neurochemical and inflammatory causes of MDMA-induced hyperthermia.

Mechan AO et al (2002) Br J Pharmacol 135(1);170–180.

Orio L et al (2004) J Neurochem 89(6):1445–1453.

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Stress-reducing effect of GABA-enriched tea in humans: assessment of stress using heart rate variability

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Introduction. GABA-enriched dietary supplements are purported to address chronic stress-induced autonomic imbalance as a risk factor for cardiovascular disease. However, there is insufficient evidence to support the effectiveness of exogenous GABA intake.
Aims. To investigate the acute effects of GABA- enriched tea in reducing stress induced by a mental arithmetic stressor in individuals, as detected by heart rate variability (HRV).
Methods. Participants were randomly allocated to consume GABA-enriched oolong tea (n=17), regular oolong tea (n=17) or water (n=17). HRV was assessed by electrocardiogram (ECG) conducted at baseline, during a 2-min mental arithmetic stressor task and after the stressor.
Results. The mental arithmetic stressor significantly decreased high frequency (HF) component of HRV (2.87±0.13 to 2.66±0.11; $p<0.05$) in the water group, while no significant differences were detected in either of the tea groups. Administration of GABA-enriched oolong tea led to a significant increase in low frequency (LF) component from 2.68±0.047 to 2.95±0.08 ($p<0.05$) during stress. While recovery from the stressor was observed in all groups, GABA-enriched oolong tea and regular oolong tea groups both exhibited increased average RR interval compared to baseline, from 863.4±24.1 to 918.0±23.4 ($p<0.01$) and 870.7±26.0 to 952.7±28.9 ($p<0.001$), respectively.
Discussion. Decreased HF in the water group during stress indicated parasympathetic nervous system (PSNS) withdrawal and sympathetic dominance in response to stress. No significant effect found in the tea groups suggested tea consumption induced stress-reducing effects, regardless of which tea was consumed. These results were consistent with the increased post-stressor average RR interval in the tea groups, indicating increased PSNS activity in reducing stress. Increased LF in the GABA-enriched oolong tea group also reflected activation of PSNS, which dominates when measured in the supine position. These data provide evidence for stress-reducing potential of teas and greater effectiveness was seen with GABA-enriched tea.

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Medication overuse headache is a manifestation of opioid induced hyperalgesia: A neuroimmune hypothesis and novel approach to treatment.

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Introduction. Patients with chronic headache who consume large amounts of analgesics are often encountered in clinical practice. Excessive intake of analgesics is now considered to be a cause, rather than simply a consequence of frequent headaches, and the diagnosis "medication overuse headache" has been formulated. Despite the prevalence and clinical impact of medication overuse headache the pathophysiology behind this disorder remains unclear and current treatment options are sub-optimal.
Aim. To explore a potential role for glial activation in the pathophysiology of medication overuse headache.
Methods. Preclinical and clinical data from the literature were reviewed.
Results. Although most acute headache treatments have been alleged to cause medication overuse headache, here we conclude opioids are the drug class most strongly associated with worsening headache. Recent evidence indicates chronic opioid administration may exacerbate pain in the long-term by non-specifically activating Toll-Like Receptor-4 on glial cells, resulting in a pro-inflammatory state that manifests clinically as hyperalgesia (Hutchinson et al, 2011).
Discussion. We hypothesise that medication overuse headache is a specific form of opioid-induced hyperalgesia, which derives from a cumulative interaction between central sensitisation, due to repeated activation of nociceptive pathways by recurrent headaches, and pain facilitation due to opioid-induced glial activation. Treatment strategies directed at inhibiting glial activation may be of benefit in the management of medication overuse headache. Potential treatment options could include agents such as ibudilast, minocycline and (+)-naltrexone.

Hutchinson MR et al. (2011) Pharmacol Rev 63(3):772-810

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Cannabinoid receptor interacting protein ($CRIP_{1a}$) modulates CB_1 receptor mediated GIRK channel activation in AtT-20 cells

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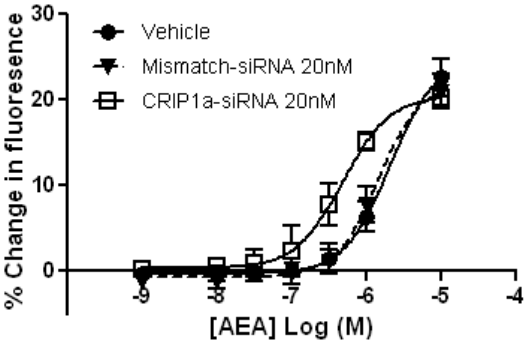
Introduction. Endocannabinoids have unique analgesic and anxiolytic properties, largely mediated by activation of the cannabinoid CB_1 receptor in the central nervous system. Cannabinoid receptor interacting protein ($CRIP_{1a}$) binds to and interacts with the C-terminal tail of the CB_1 receptor (aa 418-472) and has been shown to suppress the tonic inhibition of voltage-gated Ca^{2+} channels induced by CB_1 receptor activation (Niehaus et al, 2007). Therefore, this provides a new avenue for modulation of the endocannabinoid system. Stimulation of CB_1 receptors activates $G_{i/o}$ proteins, affecting multiple downstream signalling events including activation of inwardly rectifying potassium channels traditionally measured with biochemical assays or relatively invasive electrophysiological techniques.



Aims. To determine whether measurement of membrane potential in intact cells is a suitable assay for examining changes in CB_1 signalling in a cell line endogenously expressing both G-protein coupled inwardly rectifying potassium (GIRK) channels and $CRIP_{1a}$. Secondly, to explore the effects of $CRIP_{1a}$ knockdown on modulation of CB_1 receptor mediated activation of GIRK channels.

Methods. AtT20 cells stably expressing CB_1 were grown in 96-well microplates and serum starved overnight. Cells were incubated with a proprietary membrane potential-sensitive dye (Molecular Devices, Blue Dye) and continuous fluorescence reading obtained using a FLEX Station Microplate Reader.

Results. CB_1 receptor agonist WIN55212-2 activated CB_1, pEC50 6.8±0.1 (n=5) producing a maximum change in fluorescence of 30.54±2.31% compared to CP55940, pEC50 7.1±0.1 (n=6) which showed a maximum change in fluorescence of 27.09±1.34%. Anandamide as expected showed both a decrease in potency with a pEC50 of 5.7±0.2 (n=5) and efficacy with a maximum change in fluorescence of 20.5±1.0%. In addition, siRNA-induced $CRIP_{1a}$ knockdown significantly increased anandamide-induced GIRK channel activation (n=4, $P<0.05$).

Discussion. Given that $CRIP_{1a}$ knockdown does not have any effect on GIRK channel activation in response to WIN55212-2 or CP55940, suggests that $CRIP_{1a}$ modulates CB_1 receptor signalling in a ligand-specific manner.

Niehaus J et al (2007) Mol Pharmacol 72:1557-1566

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Mechanical hyperalgesia, but not allodynia, is sustained through α9-nicotinic ACh-receptor activity.

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Introduction. Chronic pain is poorly managed pharmacologically. Conotoxins from marine cone snails are a source of potential analgesics. Vc1.1 is an α-conotoxin producing effective, sustained relief of mechanical allodynia and hyperalgesia in rodent models of neuropathic pain. Two molecular targets could mediate these actions. Vc1.1 potently and specifically inhibits nAChRs containing α9 subunits. However, antagonism of the α9-nAChRs has been suggested to be neither sufficient nor necessary for pain relief (Nevin *et al*, 2007). Vc1.1 also inhibits N-type Ca^{2+} channel currents in a $GABA_B$ receptor-dependent manner (Callaghan & Adams, 2010), and *in vivo,* $GABA_B$ antagonists reverse acute Vc1.1 anti-allodynia (Klimis *et al*, 2011).

Aims. To determine whether or not deletion of α9-nAChRs affects the development and persistence of chronic pain in an animal model.

Methods. Several sciatic nerve injury models were tested in α9 nAChR-knockout (KO) and wild-type (WT) mice. Differences in mechanical allodynia (von Frey and incapacitance tests) and hyperalgesia (paw pressure test) were assessed.

Results: KO mice develop mechanical allodynia that is indistinguishable from WTs, which persists for at least 3 weeks. Mechanical hyperalgesia also develops in the KO within 1 week (KO: 61±67% of pre-surgical response, n=6; WT: 45±55%, n=6, $p<0.001$, Bonferroni one-way ANOVA) but greater recovery is observed by the second week post surgery (KO: 89±55 % of pre-surgical response, n=6; WT: 48±45%, n=6, $p<0.01$, Bonferroni one-way ANOVA).

Discussion. The results show that mechanical hyperalgesia is less persistent when the α9-nAChR is deleted but mechanical allodynia is unaffected. Perhaps, whilst the acute anti-allodynic effects of Vc1.1 do not involve the α9-nAChR, sustained relief of mechanical hyperalgesia may be achieved through α9-nAChR inhibition.

Callaghan, B. & Adams, D.J. (2010) Channels 4:1, 51-54
Klimis *et al* (2011) Pain 152:259-266
Nevin *et al* (2007) Mol Pharmacol 72:1406-1410

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Omega-conotoxins CVID and CVIE and two analogues display age-sensitive differences in biophysical properties in sensory neurons

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Introduction: Omega-conotoxins that selectively block N-type calcium channels are potential new therapeutics for the treating pain. We were interested in two omega-conotoxins, CVID and CVIE, which were found to have different effects in neonatal and adult rat dorsal root ganglion (DRG) neurons. Previous studies have shown that the reversibility of omega-conotoxins is dependent on differential expression of calcium channel subunits, which could potentially vary during development.

Aims: To measure the concentration-response and reversibility of omega-conotoxins CVIE and CVID in neonatal and adult DRG neurons.

Methods: Whole-cell patch clamp recordings of VGCCs was performed in isolated DRG neurons from adult (>6 weeks) and neonatal (4-12 days) male rats.

Results: Near maximal concentrations of CVID (100 nM) and CVIE (300 nM) inhibited the total I_{Ca} in all neurons (n=32) by 49 ± 4 %, with no significant difference in maximal inhibition between CVID and CVIE. In DRG neurons from adult rats, complete recovery was seen from 300 nM CVIE in all neurons (n=9). Recovery from CVID was variable, with no recovery in 4 cells, partial recovery in 1 and complete recovery in 6 out of 11 cells. In DRG neurons from neonatal rats, recovery from CVIE block was tested in two cells, with complete recovery in one and partial recovery in the other. There was no recovery from CVID in 7 neurons, and partial recovery in 1. The recovery from CVID block was significantly different in adult and neonatal neurons ($P<0.0001$).

Conclusion: Recovery from omega-conotoxin block is different in neonatal and rat DRG neurons.

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TLR2/4^{KO} mice do not display classical opioid receptor binding

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Introduction. Early opioid research focused on the stereoselective receptors that are critical for opioid analgesia. The identification of non-stereoselective opioid binding had been ignored for over 40 years and has only recently been shown to have significant behavioral importance. Toll-like receptors (TLR) have recently been identified as a potential non-stereoselective opioid receptor but existing binding data is limited and requires further investigation.
Aim. To examine both the stereoselective and non-stereoselective binding of naloxone within the mouse brain using (+) and (-) isomers. In addition, to assess the involvement of TLR2/4 in non-stereoselective binding using knockout mouse strains.
Methods. Wildtype (WT) and TLR2/4^{KO} mouse brains were fresh frozen and coronally sectioned (25μm). Sections were mounted and air-dried for 10 min. Slides were pre-incubated for 30 mins at 25°C with a protease buffer and a naloxone treatment. Slides were then incubated with a similar solution with the addition of [3H](-)-naloxone (1.636nM) for 60 mins. The tissue was washed and removed from the slides for scintillation counting.
Results. The IC50 of (-)-naloxone was 6.83nM (+/- 1.92 nM) in a naïve WT mouse brain. The (+)-naloxone isomer however was unexpectedly unable to displace (-)-naloxone. In TLR2/4^{KO} mice no (-) or (+)-naloxone binding was observed.
Discussion. These results demonstrate that using slide-mounted sections, in a naïve WT brain only stereoselective opioid binding was observed. Discrepancies in non-stereoselective binding have previously been observed between homogenate and slice-prep methods suggesting that factors required for non-stereoselective binding may be lost or not generated in the preparation of slide-mounted slices. In contrast, naïve TLR2/4^{KO} mice displayed neither stereoselective nor non-stereoselective binding for reasons unknown.

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Ciguatoxin-induced cold allodynia is an acquired peripheral channelopathy involving preferential activation of TRPA1-expressing nociceptors

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Introduction. Ciguatera is a common form of fish intoxication that typically involves several painful neuropathy-like syndromes including cold allodynia, arthralgias and myalgias. At the molecular level, ciguatoxin (CTX) is the most potent known activator of voltage-gated sodium channels. Despite the exquisite sensitivity of neurons to CTX, the precise sensory neuronal populations activated by CTX have not been determined. Specifically, it remains uncertain how CTX causes pain or how it modulates sensory inputs by altering the activity of different types of dorsal root ganglion neurons. The neuronal population activated by low concentrations of CTX may be responsible for the persistent cold-allodynia caused by ciguatera.
Aims. We sought to identify the sensory neuronal populations mediating these symptoms and to elucidate the cellular and molecular basis of ciguatoxin-induced cold allodynia.
Methods. We assessed the effects of CTX on peripheral neurons using a range of techniques including fluorescent calcium imaging of DRG neurons, animal behaviour and single fibre recordings.
Results. We show that intraplantar injection of P-CTX-1 elicits cold allodynia in mice by targeting specific unmyelinated and myelinated primary sensory neurons. These include both tetrodotoxin-resistant, TRPA1-expressing peptidergic C-fibres and tetrodotoxin-sensitive A-fibres. P-CTX-1 does not directly open heterologously expressed TRPA1, but when co-expressed with Nav channels, sodium channel activation by P-CTX-1 is sufficient to drive TRPA1-dependent calcium influx that is responsible for the development of cold allodynia, as evidenced by a large reduction of excitatory effect of P-CTX-1 on TRPA1-deficient nociceptive C-fibres and of ciguatoxin-induced cold allodynia in TRPA1-null mutant mice.
Discussion. These findings establish a peripheral site of action for ciguatoxins and reveal that altered excitability of peripheral sensory neurons can be sufficient for the development of cold allodynia.

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The influence of surgery-induced inflammation and isoflurane anaesthesia on postoperative cognitive outcome

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Introduction. The pathogenesis of post-operative cognitive dysfunction remains unclear, however, studies in young and aged animals suggest that anaesthesia and/or surgically-induced inflammation can affect cognitive outcome.

Aim. Using a rat model, we aim to investigate the role of isoflurane anaesthesia alone or with surgically-induced inflammation.

Methods. Male Sprague Dawley rats were subjected to isoflurane (n=9, 4h, 1.8% in 100% O_2). Controls were subjected to 10 min of O_2 (n=14). Laparotomy was performed in another group of isoflurane-treated animals (n=9), and the wound left open for 10min then sutured. Eight days after isoflurane exposure, cognition was tested in a fear conditioning paradigm. Rats were placed in a chamber in which they received a foot shock (1mA, 1s duration). When returned to the chamber the percentage of time spent in freezing behaviour was recorded as a measure of memory for the shock previously experienced in that chamber. One day after fear conditioning, rats were deeply anaesthetised and transcardially perfused. Hippocampal tissue was collected and processed for cytokine analysis (Bio-Plex™).

Results. Rats exposed to isoflurane showed significantly decreased freezing behaviour compared to no-anaesthesia controls, indicating a memory impairment (25.4±9.4% vs 66.21±8.9%, $P<0.01$). Rats in the isoflurane plus surgery group also had impaired memory (35.3±7.5%) but this was not worse than isoflurane alone ($P>0.05$). Isoflurane exposure was associated with increases in pro-inflammatory cytokines in the hippocampus including IL-6 and TNF-α ($P<0.05$) compared to controls and isoflurane plus surgery significantly increased TNF-α in the hippocampus ($P<0.05$).

Discussion. The finding suggests isoflurane exposure impairs memory, while additional surgical trauma does not worsen memory. Increased inflammatory cytokines in the hippocampus may be a possible mechanism behind memory impairment.

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A rapid and sensitive LC-MS method for the quantification of nilotinib in human plasma.

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Introduction. Nilotinib is a potent second-generation tyrosine kinase inhibitor used in chronic myeloid leukaemia treatment. Nilotinib plasma concentrations vary significantly between patients for a given dose, and sensitive, reproducible and efficient assays for quantifying nilotinib in patient plasma are required to support current clinical studies of optimal personalised nilotinib dosing.

Aims. To develop a rapid and sensitive LC-MS method for quantifying nilotinib in plasma, and demonstrate its application in chronic myeloid leukaemia patient samples.

Methods. Plasma samples (250 µL) were prepared by addition of d3-nilotinib internal standard, protein precipitation and centrifugation. 5 µL of supernatant was resolved with a C18 LUNA column (5 µM, 150 x 2.0 mm i.d., Phenomenex) using mobile phase (55:45 4 mM ammonium formate pH 3.2 : 0.1% formic acid in acetonitrile) at a flow rate of 0.15 mL/min. Detection was carried out on a LCMS-2010A Mass Spectrometer (Shimadzu) at *m/z* ratios of 530.10 and 533.10 for d0- and d3-nilotinib, respectively. Sample run time was 5 minutes. Steady-state trough plasma nilotinib concentrations (morning pre-dose on day 8 of treatment) were quantified in 57 chronic myeloid leukaemia patients receiving 300 mg nilotinib twice daily.

Results. Standard curves were linear from 20-5000 ng/mL ($r^2>0.998$, n=6). Intra- (n=6) and inter-day (n=6) inaccuracy and imprecision for quality controls samples (60, 30 and 1750 ng/mL) was within 14%, and within 10% for the lower limit of quantification (20 ng/mL). Nilotinib plasma concentrations in clinical samples ranged from 37 to 3470 ng/mL (median=810 ng/mL, 63% coefficient of variation).

Discussion. The LC-MS method developed has sufficient sensitivity to quantify clinically relevant nilotinib plasma concentrations within a short run time, and without the need for solid phase extraction, drying and reconstitution, or tandem mass spectrometry. The reported method is currently supporting multiple clinical trials of nilotinib in the treatment of chronic myeloid leukaemia.

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Transplacental disposition of rosiglitazone in the maternal fetal unit

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Introduction. Fetal drug exposure may be intended to treat a fetal condition or inadvertent as many pregnant women take medication potentially exposing the fetus. Despite this, the disposition of drugs that enter the fetal circulation is not well understood.
Aim: To investigate fetal placental and non-placental disposition of rosiglitazone.
Methods. In a sheep model of human pregnancy (n=7), rosiglitazone was infused directly into the fetus (2.7 mg/d) for 15 d using osmotic mini-pumps implanted subcutaneously at 128-130 d gestation (term, ~150 d). Amniotic fluid, fetal and maternal blood were collected daily from day 0 to 5, and then every 2 d until day 15. Concentrations of rosiglitazone were measured by HPLC. From the same animals, liver microsomes were used to study rosiglitazone metabolism using a substrate depletion method.
Results. The mean rosiglitazone concentration in both fetal and maternal plasma did not change significantly after day four ($P>0.05$) when steady state was reached. Fetal concentrations were an average of 1.8 fold higher ($P<0.001$) than maternal concentrations at steady state. Rosiglitazone was not detectable in amniotic fluid (<2.5 ng/mL). There was an inverse relationship between fetal AUC of rosiglitazone and placental weight ($r^2 = 0.86$, $P < 0.007$). Velocity of rosiglitazone (10 μM) metabolism in microsomes of the fetus was lower than the ewe (0.006 ± 0.002 vs 0.251 ± 0.026 μmol/min/mg). Inhibitors of CYP2C8 and CYP2C9 decreased metabolism (8.5 and 20.7%, respectively) in the ewe but not the fetus (<1%).
Discussion. Similar to adult humans, rosiglitazone had negligible renal excretion in the sheep fetus, but the renal excretion and accumulation of its metabolites in the amniotic fluid is not clear. The low oxidative metabolic capacity of the fetus indicates that non-placental drug elimination may not be well developed. It appears that the placenta remains the key eliminating organ in the fetus.

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Glucosidation and glucuronidation of mycophenolic acid (MPA) by UDP-glucuronosyltransferase (UGT) 1A and 2B sub-family enzymes

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Introduction. The UDP-glucuronosyltransferases (UGTs) are a superfamily of enzymes that primarily utilize UDP-glucuronic acid (UDP-GlcUA) as the cofactor in the clearance of lipophilic drugs and endogenous compounds from the body. However, recent data from this laboratory has shown that UGT2B7 catalyzes both the glucuronidation and glucosidation of morphine. Mycophenolic acid (MPA) has been reported to be mainly glucuronidated by UGT1A9, but it is not known which UGT enzyme(s) is responsible for MPA glucosidation which occurs in humans *in vivo*.
Aim. To characterize the comparative kinetics of MPA glucosidation and glucuronidation in human liver microsomes (HLMs) and to identify the human UGT enzyme(s) capable of glucosidating MPA.
Methods. Formation of MPA phenolic glucuronide (MPAGlcUA), MPA phenolic glucoside (MPAGlc), MPA acyl glucuronide (AcMPAGlcUA) and MPA acyl glucoside (AcMPAGlc) from incubations with microsomes from four livers (HLM) and recombinant UGT enzymes (expressed in HEK293 cells) supplemented with the appropriate cofactor (UDP-GlcUA or UDP-Glc) was quantified by HPLC with UV detection.
Results. MPAGlcUA, AcMPAGlcUA and AcMPAGlc formation by HLM followed Michaelis-Menten kinetics with an average clearances (CL_{int}) of $45.5 \pm 9.8$$\mu$L/min/mg, $8.4 \pm 1.3$$\mu$L/min/mg and $0.73 \pm 0.08$$\mu$L/min/mg, respectively. The average CL_{int} for MPAGlc formation was $5.0 \pm 2.4$$\mu$L/min/mg. The presence of both UDP-GlcUA and UDP-Glc significantly decreased the CL_{int} for MPAGlc ($0.66 \pm 0.24$$\mu$L/min/mg) and abolished AcMPAGlc formation. Screening of recombinant human UGT enzymes indicated that UGT1A9 was the main enzyme that catalyzed both the glucuronidation and glucosidation of MPA. MPAGlcUA was formed only by UGT1A family enzymes. In comparison, MPAGlc was formed by both the UGT1A family enzymes and UGT2B7. UGT1A10 and UGT2B7 were the main enzymes responsible for the formation of AcMPAGlcUA. UGT2B7 was the only enzyme found to convert MPA to AcMPAGlc.
Conclusion. Like morphine, the glucosidation and glucuronidation of MPA occur as parallel metabolic pathways but both reactions were catalysed by several enzymes from the UGT1A family.

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Mega-model of voriconazole population pharmacokinetics

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Introduction. Voriconazole is widely used in the treatment of life-threatening invasive fungal infections (IFIs). The use of voriconazole is problematic due to its highly variable pharmacokinetics and narrow therapeutic index, complicating dose selection and adjustment; few population pharmacokinetic analyses are available.
Aims. This study aimed to develop a voriconazole mega-model incorporating data from multiple studies of voriconazole pharmacokinetics in healthy volunteers and patients.
Methods. Three studies including 57 healthy volunteers with rich pharmacokinetic sampling were included in addition to sparsely sampled data from 201 patients receiving voriconazole for the treatment of IFIs. Non-linear mixed effects modelling was carried out with NONMEM 7.2; studies were added in a stepwise manner and a base model developed from the rich data; sparsely sampled patient data was then incorporated into the model. Goodness of fit criteria and visual predictive checks guided model selection and testing of covariates.
Results. Voriconazole pharmacokinetic data was described by a two compartment model with an absorption lag time and first order elimination. Coadministration of the CYP3A4 inhibitor ritonavir decreased CL by 45% (95% CI 38–53%) whereas concomitant administration of St John's wort increased CL by 122% (95% CI 85–159%); inclusion of these covariates significantly improved model fit (decrease in objective function value of –408 and –414 respectively). Voriconazole is primarily metabolised by CYP2C19; *CYP2C19* heterozygous extensive metabolisers (*CYP2C19*1/*2*) and poor metabolisers (*CYP2C19*2/*2*) had 54% (95% CI 44–65%) lower CL compared to homozygous extensive metabolisers (*CYP2C19*1/*1*). Voriconazole bioavailability was 86% (95% CI 80–91%). All model parameters were estimated with good precision (Relative SEs <16%).
Discussion. *CYP2C19* genotype is a major determinant of voriconazole disposition. Future work will utilise this model in dosing simulations and assess the feasibility of its use in a Bayesian dose forecasting tool to aid clinicians in voriconazole dose selection and adjustment.

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Cediranib and erlotinib are potent inhibitors of human solute carrier transporters

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Introduction. Members of the solute carrier family of transporters regulate the cellular influx of several drugs. OATP1A2 (*SLCO1A2*) and OATP1B3 (*SLCO1B3*) participate in the disposition of a number of anticancer drugs, including the tyrosine kinase inhibitor imatinib (Hu et al, 2008).
Aims. To evaluate the impact of tyrosine kinase inhibitors on the uptake of a prototypical substrate in cells overexpressing SLC transporters.
Methods. HEK293 cells were transfected with transporter cDNAs, including organic anion transporters (OAT1-4), organic anion transporting polypeptides (OATP1A2, 1B1, 1B3 and 2B1) and organic cation transporters (OCT1-3). Tyrosine kinase inhibitors (10 μmol/L) were tested for the capacity to inhibit the uptake of a specific transporter-mediated radiolabelled substrate into these cells. Half maximal inhibitory concentrations (IC_{50}) of potent inhibitors were determined.
Results. Of the 13 clinically relevant tyrosine kinase inhibitors tested, 11 effectively inhibited substrate uptake in some transporters. Two of these interactions had an IC_{50} in the nanomolar range: cediranib (IC_{50} of 30.6 nmol/L) and erlotinib (IC_{50} of 19.7 nmol/L) against OATP1A2 and OATP2B1, respectively. Because the maximum plasma concentration of cediranib is 0.235 µmol/L (Fox et al, 2010), this drug has the potential to inhibit OATP1A2-dependent drug transport at clinically relevant concentrations.
Discussion. The expression of several solute carrier transporters is modulated in cancer cells. Individuals with altered expression of these proteins may have different antitumour efficacy with tyrosine kinase inhibitors. Some of these agents may also elicit drug-drug interactions during therapy.

Fox E et al (2010) *J Clin Oncol* 28(35): 5174-5181.
Hu S et al (2008) *Clin Cancer Res* 14: 3141-3148.

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Liver fibrosis as the major determinant of the altered hepatic uptake of taurocholate in liver diseases

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Introduction. A number of substrates are taken up into the liver by drug transporters on sinusoidal membrane. In chronic liver diseases, the uptake of these substrates can be affected by liver transporter expression and by liver fibrosis that can arise in the space of Disse.
Aims. To examine the relative contribution of altered drug transport expression and liver fibrosis to the altered hepatic disposition.
Methods. The hepatic disposition of taurocholate was studied using in situ perfused rat liver (IPRL) in rats with a number of different liver diseases, including nonalcoholic steatohepatitis (NASH), right heart failure (RHF) and cirrhosis. The fibrosis index (FI) was used to quantify the liver fibrosis, while mRNA and protein expression of sodium-dependent taurocholate co-transporting protein (Ntcp) was determined by RT-PCR and Western Blot, respectively, to evaluate transporter function.
Results and Discussion. A good linear relationship was find between the hepatic uptake of taurocholate and FI in both the control and rat models of different liver diseases (r2=0.858). However, further stepwise regression analysis with both FI and transporter mRNA/protein expression did not significantly improve the prediction of taurocholate uptake in the liver diseases. Moreover, the good linear relationship between the reduced hepatic extraction of taurocholate and FI was also observed (r2=0.780). In conclusion, the liver fibrosis in the space of Disse is major determinant of the reduced hepatic uptake of taurocholate in liver diseases.

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In vivo bio-distribution of water-dispersible CdTe/CdS quantum dots following intravenous injection

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Introduction. Quantum dots (QDs) are potentially useful in tumour diagnosis, as bio-indicators, and in drug delivery.
Aims. To investigate the bio-distribution of water-dispersible QDs in mice following intravenous injection.
Methods. Water dispersible cadmium telluride (CdTe) QDs (~ 3.5 nm) were synthesised in aqueous solution, purified, characterised and administered to a total of 21 mice at a dose of 0.02 nmol/g by tail vein injection. At each time point (0, 5 min, 30 min, 1 h, 2 h, 8 h and 24 h), whole body fluorescence imaging (IVIS spectrum, Xenogen) was performed on 3 mice which were then sacrificed. The Cd content of heart, spleen, kidney, liver, intestine, lung, brain and blood was determined by ICP-MS after digestion with nitric acid and appropriate dilution.
Results. The QDs organ and blood concentration – time distribution profiles in organs and blood obtained using in vivo fluorescence and ICP-MS were similar but the ICP-MS was more sensitive. After intravenous injection, the QDs quickly distributed from the blood into organs with a volume of distribution of 0.185 ml/g. The clearance and elimination half-life were determined to be 0.009416 ml/h/g and 13.6 h, respectively. The spleen and liver were the main target organs for QD uptake and, in these organs, peak concentrations were reached at 1 and 2 hours, respectively. Smaller amounts of QDs were detected in heart, lung, kidney, intestine. Very low levels of QDs were found in the brain.
Discussion. Water-dispersible small QDs showed rapid uptake into various organs after intravenous dosing. Highest concentration of QDs were found in the reticuloendothelial system organs of the liver and spleen.

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Intravital imaging of fluorescein transport in the rat liver after intravenous injection

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Introduction. Intravital imaging of transport processes in the liver by multiphoton microscopy can allow the associated with the disposition of fluorescent compounds in the liver to be visualized directly in space and time.
Aims. To use intravital imaging to study how inhibitors for the uptake (Oatp) and efflux (Mrp2) hepatic transporters for fluorescein affect its hepatic disposition.
Methods. A Dermainspect multiphoton microscope with a MaiTai femtosecond laser at 920nm excitation was used to directly image fluorescein in three groups of 4 rat livers during anaesthesia after laporatomy. Rats in group 1 received intravenous injection of fluorescein (10 mg/kg) alone through jugular vein, while rats in group 2 and 3 received intravenous dosing of rifampicin (10 mg/kg) and probenecid (25 mg/kg), respectively, 10 min before administration of fluorescein. Bile samples were collected through the bile duct cannula at 10min interval until 180 min after dosing. The fluorescence intensities of fluorescein within hepatocytes were measured in time series.
Results. Fluorescein could be seen to enter the hepatocytes from the sinusoids and then relocate into the biliary canaliculae and bile ducts. Rats in group 2 and 3 had statistically lower fluorescence intensity of fluorescein in hepatocyte and had longer elimination half-life from the hepatocyte (577 min, 866 min vs 178 min), compared with rats in group 1. Co-administration of rifampicin and probenecid resulted in nearly 2 fold decrease in the cumulative amount of fluorescein excreted into the bile (24% for rifampicin and 22% for probenecid vs 43%).
Discussion. Intravital imaging with multiphoton microscopy enabled the space and time processes associated with fluorescein disposition in the rat liver to be visualised and quantified. In particular, the approached allowed the differential effects of Oatp and Mrp2 inhibition (by rifampicin and probenecid, respectively) on hepatic disposition of fluorescein examined in sinusoid, hepatocyte and bile.

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Effect of liver endothelial cell defenestration on hepatic insulin and glucose uptake

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Introduction. Fenestrations in the liver sinusoidal endothelium facilitate the transfer of substrates from blood to hepatocytes. A recent study suggested that the hepatic sinusoidal endothelium has a role in the pathogenesis of hepatic insulin resistance and the metabolic syndrome. Therefore, we proposed that a decrease in fenestrations (defenestration) impedes the transfer of insulin and glucose across the hepatic sinusoidal endothelium, thus contributing to hepatic insulin resistance.
Aims. To investigate the disposition of insulin and glucose in liver and how this is influenced by poloxamer 407 (P407), a synthetic surfactant that causes defenestration and hyperlipidemia.
Methods. Multiple indicator dilution method was performed in perfused livers of control rats (n=9) and rats injected intraperitoneally with P407, 24h prior to experimentation (1g/kg, n=8). The indicators used were Evans Blue (vascular marker), ^{3}H-sucrose (extracellular marker) and either ^{14}C-glucose or ^{14}C-insulin. Outflow samples were analyzed for absorbance at 620nm and radioactivity using liquid scintillation counter to determine substrate recovery and volume of distribution. Blood was collected prior to perfusion for lipid analysis and livers were fixed and processed for scanning electron microscopy.
Results. Animals treated with p407 showed a significant increase in triglyceride and cholesterol levels compared to control ($p<0.001$), together with a marked defenestration in the liver sinusoidal endothelial cells. The recoveries of both glucose and insulin was reduced in the hyperlipidemic rats, along with significant decreases in volumes of distribution as a fraction of sucrose for both substrates (glucose: 1.54±0.06 control vs 1.10±0.10 P407; insulin: 1.08±0.08 control vs 0.81±0.05 P407, $p<0.001$).
Discussion. P407 induced defenestration of the sinusoidal endothelium and reduced the recoveries and volumes of distribution of insulin and glucose in the liver. This finding indicates that fenestrations are important in the uptake of insulin and glucose and that defenestration may have a role in hepatic insulin resistance.

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Diurnal variation in CYP1A2 activity in individuals of South Asian and European ancestry

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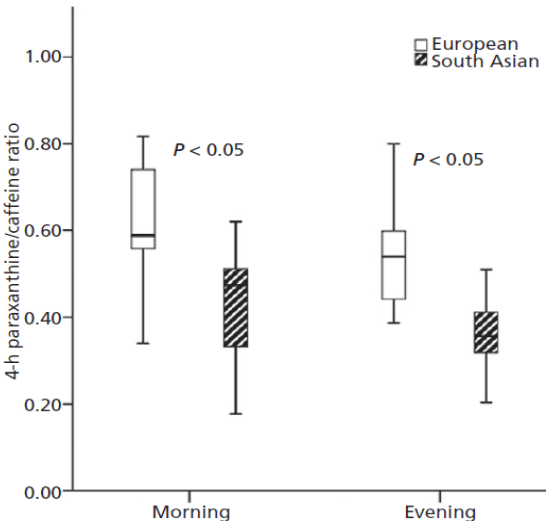
Introduction: Response to some medications can depend on time of administration throughout the day. The cytochrome P450 1A2 (CYP1A2) enzyme demonstrates wide variability which is observed in human population studies.

Aims. This study investigated diurnal variation in CYP1A2 activity in people of South Asian and European ancestry.

Methods. CYP1A2 activity was determined using the 4-h paraxanthine/caffeine saliva concentration ratio following a 100-mg oral dose of caffeine in healthy individuals of South Asian (n = 11) and European (n = 12) ancestry. Caffeine was administered in the morning and evening on three separate days.

Results. The index of CYP1A2 activity (mean ± SD) was higher in the morning (0.52 ± 0.17) when compared with evening (0.47 ± 0.17) (n = 23, P < 0.05).When stratified by ethnicity, a difference in CYP1A2 activity was observed between the morning (0.43 ± 0.13) and evening (0.35 ± 0.05) for individuals of South Asian ancestry (P < 0.05), but not in those of European ancestry (0.61 ± 0.15 and 0.56 ± 0.17, respectively). A significantly lower CYP1A2 activity was observed in South Asian participants compared to those of European ancestry in both periods (p < 0.05).



Discussion. This study observed higher CYP1A2 activity in subjects of South Asian but not European ancestry in the morning than in the evening. These results indicate that time of day may be an important consideration when administering CYP1A2 metabolised medications.

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Inhibition of human UDP-Glucuronosyltransferase 1A (UGT1A) enzymes by three different Tyrosine Kinase Inhibitors (Lapatinib, Pazopanib and Sorafenib): implications for drug interactions and jaundice

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Introduction. Tyrosine kinase inhibitors (TKIs) are of proven efficacy in the treatment of a number of cancers: e.g. sorafenib for kidney and liver cancers; lapatinib for breast cancer and pazopanib for kidney cancers and sarcoma. Patients receiving TKIs are at risk of drug interactions due to polypharmacy. However, the potential of TKIs to perpetrate drug-drug interactions remains to be fully characterized.

Aims. To characterize the inhibitory effects of lapatinib, pazopanib and sorafenib on the activities of UGT1A sub-family enzymes to assess the likelihood of clinically significant inhibition *in vivo*.

Methods. Recombinant human UGT1A enzymes and human liver microsomes (HLMs) were utilized as the enzyme sources. Inhibition of recombinant UGT1A enzyme activities was assessed at 4 different TKI concentrations (0.01, 0.1, 1 and 10 μM) using 4-methylumbelliferone (4MU) as the probe substrate (Uchaipichat et al., 2004). Kinetic experiments for sorafenib inhibition of bilirubin glucuronidation were performed.

Results. Sorafenib (10 μM) inhibited all UGT1A enzymes. IC_{50} values for UGT1A1, UGT1A7, UGT1A8 and UGT1A9 were < 1 μM. Derived IC_{50} values were 0.051 μM, 0.034 μM, 0.031 μM and 0.039 μM for wild-type UGT1A1-HLM, UGT1A*28-HLM, wild-type UGT1A1, and UGT1A1*6, respectively for bilirubin glucuronidation. Pazopanib inhibited UGT1A1, UGT1A7, UGT1A8 and UGT1A9 with Ki values <10 μM. Lapatinib showed similar inhibition of UGT1A1, UGT1A3 and UGT1A9.

Discussion. All the three TKIs (lapatinib, pazopanib and sorafenib) are potent inhibitors of UGT1A1 with Ki values < 2 μM. Current data indicate that there is a potential for the screened TKIs to cause inhibition of UGT1A1 specific substrates like bilirubin. This is consistent with the clinical finding of drug induced jaundice by these TKIs.

Uchaipichat V et al (2004) Drug Metab Disp 32:413-423

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***In vitro* characterisation of the 'albumin effect' on human liver microsomal olanzapine oxidative metabolism**

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Introduction. Olanzapine (OLZ) is an atypical antipsychotic commonly prescribed for the management of schizophrenia and related psychosis. Although there is wide inter-individual variability in OLZ pharmacokinetics and response, the metabolism of OLZ is incompletely characterised and CYP1A2 is thought to play a significantly role. Thus, factors that influence the clearance of OLZ, and subsequently maintenance dose to attain therapeutic steady-state concentration, are poorly understood.
Aims. To investigate the 'albumin effect' on the oxidative metabolism of OLZ in human liver microsomes (HLM).
Methods. A UPLC-MS method was developed and validated to quantify OLZ and its three oxidative metabolites (*N*-desmethyl-, hydroxy-, and *N*-oxide-olanzapine). Assay conditions were validated with respect to incubation time, protein concentration, and reproducibility. The kinetics of OLZ metabolite formation (K_m and V_{max}) were characterised in the presence and absence of bovine serum albumin (BSA; 2%). Binding of OLZ to incubation components was accounted for in the calculation of kinetic parameters. Whole liver intrinsic clearance ($CL_{int.liver}$) was predicted using hepatic scaling factors.
Results. In the absence of BSA, OLZ *N*-demethylation and *N*-oxidation were best described by the Michaelis-Menten equation. $CL_{int.liver}$ values for these pathways were 4.7 and 1.5 L/h, respectively. The OLZ hydroxylation pathway was best described by the 2-enzyme Michaelis-Menten equation; with a combined $CL_{int.liver}$ of 0.8 L/h. In the absence of BSA, the total $CL_{int.liver}$ for HLM catalysed OLZ oxidative metabolism was 7.0 L/h. Addition of BSA caused a 2-fold increase in total HLM catalysed OLZ metabolism, primarily due to a reduction in K_m for the N-demethylation and *N*-oxidation pathways. The total $CL_{int.liver}$ in the presence of BSA was 13.5 L/h.
Discussion. These data indicate that *N*-demethylation is the primary oxidative pathway for OLZ. The 'albumin effect' increases the *N*-demethylation and *N*-oxidation of OLZ and results in a 2-fold increase in predicted whole liver intrinsic clearance.

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Allometric scaling of antimalarial drugs

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Introduction. World Health Organization and pharmacopoeial dosage recommendations for most antimalarial drugs are the same (mg/kg) for children and adults. However, the clearance (L/h/kg) for many drugs is higher in children than in adults and there is recent evidence that children require higher chloroquine doses (mg/kg) compared to adults for optimum clinical outcome (Obua et al, 2008,Moore et al, 2011).
Aims. Conduct interspecies allometric scaling of CL and V for selected antimalarial drugs and investigate the interpolation of CL data for dose predictions in children.
Methods. Pharmacokinetic data (CL and V) for antimalarial drugs in healthy and malaria infected species were collated. Regression analysis of log-transformed data was performed to determine the coefficient (a) and exponent (b) for the allometric equation, $Y = a \times Wb$, where Y is the pharmacokinetic parameter and W is body weight. The exponent for CL and the recommended adult dose were used to predict a scaled dose for a 25 kg child.
Results. A paucity of data (< 3 species) precluded scaling in malaria infection and restricted the range of drugs investigated. Exponents for CL of quinine, mefloquine, clindamycin and dihydroartemisinin in healthy species were 0.4, 0.52, 0.63 and 0.8 respectively (r2 >0.9) and the exponents for V were 0.88, 0.78, 0.8 and 0.8, respectively (r2 >0.9). The predicted child doses for quinine, mefloquine, clindamycin and dihydroartemisinin were 84%, 64%, 46% and 14% higher (mg/kg for 25 kg child) than adult doses.
Discussion. Our data indicate that higher mg/kg doses of some antimalarials are required for children. The doses should be determined for individual drugs, with consideration of altered pharmacokinetic properties in malaria infection, and not based on a universal, fixed exponent.

Obua C et al (2008) Br J Clin Pharmacol 65:493–501
Moore BR et al (2011) Antimicrob Agents Chemother 55:3899–3907

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Combinational therapy with oxycodone and zoledronic acid in inflammatory arthritis: The role of cytokines in acute and chronic inflammation.

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Introduction: Cytokines that are abundantly produced in inflamed rheumatoid synovial fluid, such as tumour necrosis factor α (TNF-α), interleukin-1β (IL-1β), and IL-17, play crucial roles in the pathophysiology of rheumatoid arthritis (RA). Bisphosphonates inhibit bone destruction and are shown to increase bone density in animal models of RA while opioids are used as adjunct drugs for analgesia and are also known to have anti-inflammatory effects.
Aims: To investigate the role of inflammatory cytokines in the mechanism of action of oxycodone and zoledronic acid (ZA) in attenuating acute and chronic inflammation.
Methods: Dark Agouti (DA) rats were induced with adjuvant arthritis by inoculation with Freund's complete adjuvant either into the right hind paw or the base of the tail to induce mono and poly arthritis respectively. Oxycodone and ZA were administered at different doses and time intervals. Immunohistochemistry was utilised to determine the localisation of inflammatory cytokines in rat ankle joints.
Results: Combination therapy significantly reduced bone damage and showed analgesic effects. Oxycodone and ZA in combination proved to be very effective in combating arthritis by reducing inflammation and pain as well as inhibiting bone damage. Individual treatment reduced arthritic severity by 81% and 63% at an optimum dose of oxycodone 5mg/kg and ZA 3μg/kg respectively. Combinational therapy was effective in reducing arthritic severity at a lower dose than individual therapy; the optimum dose combination was oxycodone 5 mg/kg and ZA 1μg/kg. Paw pressure thresholds significantly decreased in treated arthritic rats ($P<0.05$), while control animals showed significant hyperalgesia. The treatment also reduced the levels of the proinflammatory cytokines TNF- α, IL-1 β beta and IL-17 in the tibial- tarsal joint as compared to controls. Conclusion: The results suggest that combining oxycodone and ZA has a potential therapeutic relevance in the treatment of arthritis.

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Choice of contractile agonist influences dilator efficacy in small airways in mouse lung slices

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Introduction. Altered reactivity of small airways may contribute to airway hyperresponsiveness and reduced β_2-adrenoceptor sensitivity in severe asthma. It is therefore important to characterise small airway contraction to diverse agonists, such as methacholine (MCh) and endothelin-1 (Et-1); the latter being markedly increased in treatment-resistant asthma (Pegorier *et al*., 2007). These constrictors can then be used to assess the relative efficacies of bronchodilator therapies.
Aim. To assess the influence of contractile stimuli, MCh and Et-1, on small airway relaxation to salbutamol (SAL), prostaglandin-E_2 (PGE_2) and novel bronchodilator rosiglitazone (RGZ).
Methods. Changes in small airway lumen area were measured in lung slices (150 μM) from 6-8 week old male Balb/C mice. After characterising contraction to MCh and Et-1, dilator responses were assessed at varying levels of pre-contraction.
Results. Et-1 was 19-fold more potent than MCh (pEC_{50} 8.5 ± 0.1, 7.1 ± 0.1 respectively, $p < 0.05$), and both reduced airway lumen area by up to 50%. The rank order of dilator potency was PGE_2 > SAL > RGZ, where maximal relaxation of ~75% was achieved by RGZ against both constrictors. PGE_2 and SAL were markedly less effective than RGZ in relaxing Et-1 pre-contraction, and β_2-mediated relaxation completely abolished in maximally contracted airways.
Discussion. Et-1 is a potent constrictor of mouse small airways. SAL was the least effective of the dilators tested. Although PGE_2 was the most potent, RGZ was as effective as PGE_2 against MCh, and more effective against Et-1. This study emphasises the need to explore the clinical potential of novel dilators against multiple contractile agonists implicated in human asthma.

Pegorier *et al* (2007). JACI **120:** 1301-1307.

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Effect of anti-oxidants on influenza A infection in cigarette smoke-exposed mice

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Introduction. Influenza virus infections are a common cause of chronic obstructive pulmonary disease (COPD) exacerbations. Oxidative stress and reactive oxygen species (ROS) have been implicated in COPD and influenza virus-induced lung inflammation. Targeting oxidative stress and ROS production may be a novel way to treat acute exacerbations of COPD.

Aim. To evaluate the effect of the anti-oxidants ebselen and apocynin on the outcome of influenza A infection in cigarette smoke (CS)-exposed mice.

Methods. Male Balb/C mice were exposed to CS generated from 9 cigarettes per day for 4 days. On day 5, mice were infected with $1x10^{4.5}$ PFU of the influenza A virus Mem71 (flu, H3N1). BALF inflammation, viral titre, and whole lung cytokine, chemokine and protease mRNA expression were assessed 3 days post infection. Body weight and food intake were measured daily. Mice were treated with the anti-oxidants ebselen (10mg/kg, oral gavage) or apocynin (5mg/kg, i.p.) 3 h before infection and then daily thereafter.

Results. Compared to mice exposed to CS or treated with flu alone, CS+flu mice had a significant increase in BALF total cells, neutrophils and lymphocytes ($n=6$, $p<0.05$). Gene expression analysis revealed that CS+flu mice had increased levels of pro-inflammatory cytokines (Csf3, IL-16), chemokines (CxCl10, Cxcl9) and proteases (MMP-12), compared to CS or flu alone mice. However, ebselen and apocynin did not reduce the enhanced BALF inflammation observed in CS+flu mice ($n=6$, $p>0.05$), nor pro-inflammatory cytokine, chemokine and protease expression. Similarly, ebselen and apocynin did not have a significant effect on viral clearance in CS+flu-treated mice ($n=6$, $p>0.05$), nor did they affect CS-induced weight loss and food intake.

Discussion. These data indicate that in this animal model of cigarette smoke and influenza A (H3N1) infection, the anti-oxidants ebselen and apocynin do not reduce acute exacerbations of CS-induced lung inflammation induced by influenza A infection.

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Investigating the role of PTEN in airway epithelial inflammation and remodelling in Chronic Obstructive Pulmonary Disease (COPD)

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Introduction. COPD is characterised by chronic airway inflammation that compromises the integrity of the airway epithelium. PTEN, which acts as a negative regulator of multiple signalling pathways, has shown to be reduced in COPD airway epithelial cells. However, its implications on epithelial inflammation and remodelling in COPD have not been investigated.

Aims. To develop an efficient method that reduces PTEN expression in human bronchial epithelial (Beas-2B) cells, using siRNA and determine whether this has a functional effect on the expression of inflammatory mediators, such as Interleukin-8 (IL-8) and Serum Amyloid A (SAA), initiated by Toll-like Receptor (TLR) signalling pathways.

Methods. To reduce PTEN expression, Beas-2B cells were cultured, harvested and resuspended in low serum optiMEM media. Using a 6-well format NeoFx siport (Ambion) transfection reagent was used to reverse transfect cells with PTEN siRNA (Life Technologies), in accordance with the manufacturer's instructions. Cells were transfected with Control siRNA as control. To determine whether the loss of PTEN enhanced inflammatory markers, cells were stimulated with 100ng/mL Lipopolysaccharide (LPS) and treated with 10^{-7}M Budesonide (BUD). The cell pellet was collected and stored at 3h and 48h post treatment.

Results. Using Q-PCR (Life Technologies), a 70% reduction ($n=6$, $p<0.05$) in PTEN mRNA levels was achieved. Western blot analysis measured PTEN and p-Akt protein levels. A 50% reduction ($n=2$) in PTEN protein was observed, which was associated with elevated p-Akt at baseline after LPS stimulation ($n=2$). Reduced PTEN expression did not alter gene expression of the selected inflammatory mediators.

Discussion. A method for efficient PTEN knockdown using siRNA and reverse transfection was successfully developed. This data suggests that the loss of PTEN does not enhance LPS-induced inflammation. However, we are currently investigating whether reduced PTEN expression alters markers of epithelial to mesenchymal transition (EMT) that may contribute to airway narrowing/fibrosis in COPD.

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Effectiveness of a blended learning approach in delivering advanced drug delivery systems to third year pharmacy students at Curtin University

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Introduction. In order to effectively deliver advanced pharmaceutical technology topics to enhance students' knowledge, a blended learning approach that comprised lectures, practical and workshop sessions was designed and piloted as part of the teaching program for third year Pharmacy students at Curtin University. .
Aims. The aim of the project was to evaluate the effectiveness of the blended learning approach in enhancing students' understanding and knowledge and to determine the level of its acceptance by students.
Methods. Students were given three standard lectures on advanced drug delivery systems, followed by a 3 hour practical session and a 2 hour workshop. For each practical session, students were divided into groups undertaking preparation and characterisation of nanoparticles, liposomes and microcapsules. Prior to the practical session, students completed a multiple choice question (MCQ)-based test to assess their knowledge of the topic. Follow-up workshops were conducted after the practical session. The workshops included facilitated discussion amongst students and the whole class, group poster work, a post-laboratory MCQ test and a written evaluation of the DDS sessions.
Results. The average score for the pre-laboratory test was 66.4%±0.7% (n = 107) and for the post-laboratory assessment using the same set of questions was 82.1%±0,9% (n = 107) with most scoring perfect marks. The average score for a new set of 5 questions was 78.7±1.0% (n = 107). In the evaluation, most students indicated that this learning method provided them with a better appreciation of the theory and principles of drug delivery and facilitated their learning.
Discussion. The feedback from students suggests the blended learning approach is effective in optimising the students' overall learning process and improves student understanding of physical pharmacy theory and its application. Students' performance in assessment was shown to have improved as a result.

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Evaluation as best practice: a case study on interdisciplinary learning and teaching of a Remote Health Experience program at Flinders NT.

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Introduction. Achieving meaningful interprofessional learning is a challenging goal. The Remote Health Experience is part of the year one Medical course; a team of interdisciplinary academics designed and implemented an interdisciplinary program where students from medicine, pharmacy, aboriginal health worker courses and nursing degree, would be combined and would practice skill stations as multidisciplinary groups. In 2011 the first Flinders NT program was launched and interdisciplinary teams of participants (teachers and learners) engaged in the activity. The 2012 program was redesigned to incorporate the feedback collected from the 2011 evaluation completing the loop for responsive quality improvement.
Aims. This presentation will describe the key aspects of the two-year interdisciplinary educational program evaluation and demonstrate the importance of program evaluation.
Methods. The evaluation integrates process evaluation into a continuous, and thus responsive, quality assurance model using anonymous and voluntary surveys given to all participants after each station and at the end of the program. The 2011 results were incorporated into the 2012 program that was re-evaluated using the same instruments.
Results. In 2012, the response rate was 85% against 65% in 2011. In 2012, student participants rated the skill stations higher (5 and 4 on a Likert scale) against an average rating of 3 in 2011. Learning objectives were reported enhanced by the interdisciplinary activity by 92% of the participants (learners and teachers) in 2012, against 63% in 2011. In 2012, 95% of participants strongly agreed on the quality of the delivery while only 58% agreed in 2011.
Discussion. The participant students stated the benefits from the interdisciplinary learning program and the teachers reported an enhancement of their teaching skills by practising in an interdisciplinary team. Evaluation was key in informing what works best by providing feedback for an improved 2012 program.

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The eBook 'Pharmacology in one semester: uses and student evaluation

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Introduction. The eBook 'Pharmacology in One Semester' is an unpacked/simpler version of pharmacology for use with Biomedical/Medical/Science or Allied Health students, who are undertaking an introductory unit, or one unit in total, in Pharmacology. It was designed to have flexibility in content, and allow the teacher to modify the content to suit their teaching style and/or the cohort. The eBook is freely available (from sheila.doggrell@qut.edu.au) and has been distributed nationally and internationally.
Aims. The aims were to determine (i) how the eBook was being used in Australasia, and (ii) how the students evaluate it.
Methods. A request was emailed to academics with an interest in using the eBook, asking how they had used it, and if they had evaluated it.
Results. The eBook is being used as a resource for students and staff. Thus, JH and JL provide the eBook as a resource for their allied health students (nursing, midwifery, podiatry, paramedic, chiropractic, osteopathy and Chinese medicine students), but do not know whether the students are using it. DM uses the eChapters on Drugs & the Gastrointestinal Tract, and Drugs & the Respiratory as a resource for pharmacy students, and has shown that it was accessed often, and this access is probable to download the eBook. EP has used the eChapters on Drugs & Hypertension and Anti-infectives as the basis for overviews of these topics on their ePharmacology site. SD uses the eBook as the basis of her lecturing to Allied Health students, and releases the eChapters after the lecturing. The students use the eChapters in their preparation for tutorials and exams, and it is very popular.
Discussion. Presently, the eBook 'Pharmacology in One Semester' is being used as envisaged by the authors, but has not been taken up widely. More evaluation of the eBook is required.

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Quality assurance exercise for assessing basic compounding skills of pharmacy students

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Introduction. Pharmaceutical compounding is a core skill for pharmacists. At Curtin University, pharmacy students compound a range of preparations that are assessed by observation of technique, accuracy of records produced and visual appraisal of product quality, but not analysis to quantify the content of active ingredient.
Aims. This study sought to develop compounding laboratory preparations that could be rapidly analysed for content of active ingredient and to investigate the ability of first year pharmacy students, after one semester of training, to accurately prepare simple solutions using weighing, measuring and calculation skills.
Methods. Lignocaine Hydrochloride was identified as a suitable test substance. Laboratory students were instructed to prepare two solutions of Lignocaine HCl 0.025%, one from the drug powder involving the preparation of an aliquot and the other a dilution of a concentrated solution. The solutions were analysed by uv spectrophotometry.
Results. A concentration of 0.025% ± 10% was considered acceptable. Only 47 of 94 students (50.0%) who completed the aliquot solution produced solutions of acceptable concentration. Five (5.3%) students had miscalculated, leaving 42 (44.7%) with deficiencies in weighing and/or measuring skills. 65 of 93 students (69.9%) completed the dilution exercise with acceptable accuracy.
Discussion. This simple exercise demonstrated the inability of a significant proportion of students to accurately compound simple solutions, reflecting the findings of Kadi and co-workers (2005). Deficiencies in students' weighing and measuring skills were revealed. A greater proportion of students were able to accurately perform the dilution task than the more complicated aliquot solution. The potency analysis provides a powerful teaching tool, via prompt feedback, to encourage students to reflect on, and improve their techniques. This exercise can be employed as a quality assurance measure at any point during pharmaceutical compounding training.

Kadi A et al (2005) Am J Pharm Ed 69: 508-515.

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What really makes students 'work ready' – what are pharmacy students' and their preceptors' considerations?

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Introduction. Comprehensive, first-hand understanding of the concept of pharmacy students' 'work readiness' is vital for academic educators, pharmacy preceptors, and pharmacy students. This can enable academic institutions to provide pharmacy graduates with informed learning strategies that will result in an optimal set of necessary graduate attributes, enabling them to thrive in the increasingly competitive pharmacy market.
Aims. To explore understanding of the concept of 'work readiness' amongst the pharmacy students and their preceptors in order to inform future teaching initiatives, particularly in the area of work-integrated learning.
Methods. Community pharmacy preceptors (92) were visited during regular 4th year placement visits by the Griffith University School of Pharmacy Placements Team (two Placements Coordinators, an Associate Lecturer, and the Course Convenor). Preceptors were asked what they believed, in general, constituted 'work readiness' in pharmacy interns and their responses were recorded in writing by the visiting Placements Team members. Seventy-one Pharmacy students were asked to reflect and elaborate on what they believed made them 'work ready'. This survey took place in the lecture, was voluntary and anonymous, and the answers were provided in writing.
Results. In addition to the importance of students' basic clinical and practice knowledge for their work readiness, the Preceptors' responses particularly emphasised the value of 'soft', transferrable skills in pharmacy graduates (e.g. team work, awareness of workplace dynamic, 'good personality', hardworking enthusiastic attitude), and believed that these skills could not always be 'learnt at university' but instead needed to be gained through experience or are sometimes simply individual student's innate traits. Students' responses were similar to the Preceptor ones, also further emphasising the value of good communication skills, accepting constructive criticism, friendliness, personality, and willingness to learn.
Discussion. Our findings have major implications for optimisation of our Pharmacy curricula, in particular design of their work-integrated and career development components.

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Competency standards come to life for UTAS Bachelor of Pharmacy undergraduates

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Introduction. Pharmacists use competency standards (CS) [1-2] to attain their right to practice and ensure they continue to review their practice for life. Currently the CS are not well articulated to students in the UTAS BPharm undergraduate curriculum.
Aims. Establish current student awareness, understanding and use of the CS. Provide undergraduate students input in the review and development of their curriculum.
Methods. Using mixed methods UTAS Pharmacy students were surveyed.
Results. A student survey revealed that students do see the CS as important to their studies and assumed they were already considered in designing their curriculum.

Question	Yes
Do you know what the CS are?	65%
Year 1	93%
Year 2	14%*
Year 3	89%
Year 4	93%
Do you think CS are relevant to you now?	67%
Do you think CS will be relevant to you in the future?	87%
Do you refer to the CS to chart your own progress currently?	12%

*P < 0.0001; Students in the current 2nd year BPharm cohort have not received anything on CS in the curriculum.
Discussion. The CS will be further articulated in the UTAS BPharm degree through the development of a validated tool that will assist staff in the review and design of their current units. This process will lead to increased discussion between staff, assist with accreditation requirements and improve benchmarking opportunities with other Schools nationally and internationally.

1. Competency Standards Review Steering Committee, National Competency Standards Framework for Pharmacists in Australia. 2010.
2. Advanced Pharmacy Practice Framework Steering Commitee, Professional Practice Profile for Initial Registration as a Pharmacist. 2011.

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The UTAS pharmacy students' road map

Rose Nash[1], Gregory Peterson[2], Natalie Brown[3], Shane Jackson[4]. School of Pharmacy, Univ of Tasmania[1,2,4], Hobart, TAS, TILT, University of Tas[3], Hobart, TAS.

Introduction. The School of Pharmacy UTAS has introduced a road map for undergraduate students and staff.
Aims. A flow chart was designed to show students the pre-requisite subjects required for each unit and where their current units would feed into the next semester and year. By mapping the units to the competency standards [1-2] students would be able to have a long-term vision, and recognise the continuity between their first year of study in the Bachelor of Pharmacy (BPharm) through to registration and practice as competent pharmacists.
Methods. In 2012 a flow chart and case study were included in all BPharm unit outlines. Students were surveyed regarding their knowledge and awareness of the competency standards and their acceptance of the flow charts. Themes identified in surveys were further developed in student focus groups.
Results. The flow chart and case study have been embraced and integrated by staff, and welcomed by our students. All the units in the BPharm degree have been mapped to ascertain if the competency standards had been addressed adequately or if there was unnecessary duplication.

Question	Yes
Do you feel unit coordinators referred to the competency standards when developing units?	67%
Do you think it (flow chart) should remain in the unit outline?	67%

Discussion. The course will be reviewed in line with the competency standards to ensure our students are closer to readiness to practice at the successful completion of the BPharm degree.

1. Competency Standards Review Steering Committee, National Competency Standards Framework for Pharmacists in Australia. 2010.
2. Advanced Pharmacy Practice Framework Steering Commitee, Professional Practice Profile for Initial Registration as a Pharmacist. 2011.

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Competency of Pharmacy graduates-tool validation and investigation

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Introduction. The pharmacy profession has developed a framework which sets the practice standards for the profession. This framework outlines competency standards (in domains) that professionals within the field should reach. These are expected to be well developed in the undergraduate degree, and throughout the intern year. At this time, there exists no formal tool for assessment of these competencies.
Aims. To validate a questionnaire for use as a tool to assess the competence of pharmacy graduates, and, to investigate the competence of La Trobe University Pharmacy graduates.
Methods. A cross-sectional descriptive study using a quantitative approach was employed. A 56-item questionnaire was sent to employers or preceptors of La Trobe University pharmacy graduates. Data analysis involved descriptive statistics and Rasch analysis through the statistical packages SPSS and RUMM 2030 respectively.
Results and Discussion. Questions for each domain showed high Cronbach's α values (0.843- 0.960), suggesting very good internal consistency of the scales, with some redundancy. High correlating items were identified and deleted from domain, the α values (0.843-0.949) did not significantly change, suggesting their exclusion may not adversely affect overall results. This was confirmed through Rasch analysis, with the changes in PSI values not significantly altering with question deletion. Thus the 56 item questionnaire may be reduced to 50 items without loss of integrity. Overall competency for La Trobe University graduates was found to be high. Total scores for domains of Professional and ethical practice, Review and supply prescribed medicines, Prepare pharmaceutical products, Promote and contribute to optimal use of medicines, Critical analysis, research and education were high, with medians ranging from 3.99 to 4.29. Scores for domains of: communication, collaboration and self-management; leadership and management, and deliver primary and preventive health care were lower with medians ranging from 3.67 to 3.84. Most respondents (94%) said that they would recommend La Trobe graduates to other supervisors or employers. This together with the relatively high competency scores suggests that as a whole, graduates meet the professional practice standards.

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Jack and the Beanstalk, Climbing the Vine of Skills – Preceptor Training for Pharmacists

Catherine Spiller, Marika Castrisios, Lisa Crisp, (School of Pharmacy UTAS, Hobart, Tasmania)

Introduction. The Tasmanian school of Pharmacy has clinical placements in the third and fourth year of the course. We utilize a large number of placement sites in community and hospitals in Tasmania and rely on practicing Pharmacists to act as preceptors for our students. As pharmacy student numbers have increased over recent years, so has the need for quality clinical preceptors. Feedback was sought from existing pharmacist preceptors on the barriers to taking on students for clinical placements. From this, training needs were identified and a two hour, group two accredited CPD session was developed for delivery to pharmacists in three locations across Tasmania.

Aims. The aims of this training package were; to provide formal, accredited CPD to existing preceptors free of cost as a thank you for their contribution to training UTAS students; and to support preceptors in their role by giving formal training in preceptor skills.

Methods. A review of the literature and current preceptor training programs was undertaken. Relevant stakeholders were consulted with regards to potential content and delivery style. The authors researched and developed the training material, arranged and marketed three events. The presentation covered learning styles, general preceptor skills and cultural competency.

Results. The sessions were well attended with 61 pharmacists attending statewide. Evaluation of the activity by attendees showed; 96.7% agreed or strongly agreed that the CPD met the specified learning objectives, 95% agreed or strongly agreed that the CPD activity was worthwhile and 96.7% agreed or strongly agreed that the knowledge gained through participation will impact on their practice.

Discussion. Very few pharmacists receive formal training as preceptors but this need can be well met by universities. By supporting preceptors in their role universities can strengthen ties with the pharmacist workforce, hopefully ensuring the availability of quality clinical placement opportunities into the future.

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Supporting Tasmanian hospital pharmacists to mentor pharmacy students

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Introduction. With increased pharmacy student numbers hospital pharmacy departments are being asked to take on more students than in previous decades. For partnerships between the university and these hospitals to remain strong additional support from the university is required.

Aim. The aim of project was to increase clinical placements in Tasmania for Pharmacy students at hospital sites in Tasmania.

Method**.** Input was sought from pharmacists across the four hospital sites to determine what barriers existed to taking on students, what challenges were faced by pharmacist preceptors and how the university could provide improved support to these pharmacists and their students. Using this information several trial strategies were developed which included;

- Timetabling support
- Fostering inter-departmental relationships to establish interdisciplinary student learning opportunities at NWRH.
- Production of a student workbook to guide pharmacist preceptors and facilitate communication between students and pharmacists, being trialled at two sites
- Independent project sheets for the students to complete when workload or staffing pressures limit a pharmacist's availability for constant direct supervision of the student. Being trialled at 3 sites.
- Feedback surveys for the department to gather responses from the students about the success of the hospital pharmacy's student placement program, being trialled at all sites.

Results**.** Evaluation of all trial strategies has been carried out. Preceptors and students have been asked to participate in the evaluation; these will be available for the conference by mid October.

Discussion. Anecdotally the resources and support has been well received by both pharmacists and pharmacy students and we look forward to the results of the evaluations.

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Fostering deep learning through collaborative learning and peer assessment: A case study in Pharmacology Teaching and Learning.

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Introduction. Peer assessment and collaborative learning have been shown to improve students understanding of the assessment process (Bloxham & West, 2004). The main challenge for teachers of pharmacology is to transform students' perceptions from 'pharmacology equals an extensive amount to know and remember' to 'pharmacology equals an interesting and essential subject that enhances competency in both clinical pharmacology and the prescription of medications'.
Aims. Acknowledging that assessment drives learning and that assessment play a major role in shaping student's perception of learning, collaborative learning and peer assessment were implemented in this study to enhance pharmacology learning.
Methods. The study was conducted in 5 stages. Stage 1: Students worked collaboratively to review lectures. Stage 2: Students formulated questions accompanied with clear marking keys. Stage 3: Moderation of questions. Stage 4: Peer assessment and peer feedback. Stage 5: Evaluation of teaching method.
Results and discussion. In this study involving 218 students, all who have participated in the survey (67 responses) has agreed that the collaborative learning in Stage 1 has enhanced their understanding and deepened their knowledge of Pharmacology. Using the Likert scale, there is 94% agreement that the combination of collaborative learning, exam preparation and peer assessment has helped them developed critical thinking in relation to pharmacology knowledge; 88% and 91% agreement that the activities are engaging and have motivated them to learn, respectively. Students have agreed that the process has helped them remember the content in pharmacology (90% agreement), deepen their knowledge and understanding of pharmacology (89% agreement), increased their confidence in their ability to understand pharmacology and complete the test (89% agreement) and has clarified the assessment criteria (91% agreement). The students suggested the peer assessment to be a closed book test for best result.

Bloxham, S & West, A (2004) Assessment and Evaluation in Higher Education, 29(60), 721-723.

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Adding creativity to pharmacy practice: Using Bloom's Taxonomy to develop learning skills in fourth year pharmacy students.

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Introduction. It is essential for students to have an understanding of factual knowledge for medication therapy management, however students must able to integrate this knowledge and apply it to unfamiliar scenarios. The cognitive process dimensions of the revised Bloom's Taxonomy states that if a student can function at the creating level, they have mastered the ability to remember and apply knowledge.
Aims. To evaluate graduating pharmacy students' attitudes of creating and analysing problem-based learning activities in medication therapy management.
Methods. Students were introduced to the concept of Bloom's Taxonomy in lectures. Structured activities to create problem-based learning problems were completed during tutorials for the disease states covered during the semester to complement traditional knowledge and application tasks. The created problems were analysed and critiqued by peers to assess accuracy and relevance of these activities. A survey instrument was administered anonymously in September 2012 to graduating pharmacy students at the Queensland University of Technology.
Results. The majority of students (97%) agreed or strongly agreed that creating problem-based learning activities enhanced their learning of medication therapy management and (89%) analysing these created activities enhanced their learning. Thematic analysis of the qualitative data reported that this activity assisted students to integrate previous knowledge and understand the relevance of therapeutic issues in medication therapy management.
Discussion. The systematic and structured integration of activities requiring students to perform skills from the high cognitive processes was accepted by students who perceived that it enhanced their learning of medication therapy management.

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Parents' perspectives about factors influencing adherence to pharmacotherapy for attention-deficit hyperactivity disorder (ADHD)

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Introduction. Pharmacotherapy is commonly used to control symptoms associated with attention-deficit hyperactivity disorder (ADHD). Parents who elect to commence pharmacotherapy for their children are responsible for medicine-giving in up to 84% of cases. However, adherence rates decrease to 50-75% within 12 months of treatment initiation. Children who do not continue pharmacotherapy experience symptom relapse and overall deterioration of their condition.

Aims. To explore factors influencing parents' decisions to adhere and persist with ADHD pharmacotherapy.

Methods. Focus groups (n=3), lasting 1-1.5 hours, were conducted with 16 parents recruited from metropolitan Sydney areas by a market research company. The group discussions explored factors that impacted upon initiation, continuation and cessation of therapy. Focus groups were audio-recorded, transcribed verbatim and thematically content analysed.

Results. Parents commenced and continued pharmacotherapy due to its impact on their child's behavior, with symptom improvement often observed within a few hours of medicine initiation. Notable improvements in the child's academic performance and social interactions motivated parents to persist with therapy. Many parents elected to cease therapy after their children experienced side effects, including appetite suppression, weight loss and sleep disturbances. Concerns about the long term effects of ADHD medicine use including potential for addiction and growth stunting; stigma associated with the condition; criticisms of their parenting skills; and questioning of their motives for medicating their children, also contributed to parents ceasing treatment.

Discussion. Several factors impacted upon parental decisions to adhere and persist with pharmacotherapy for ADHD. Short and long term side effects of medicines along with stigmatising experiences faced by parents played a large role in discontinuation of treatment, whilst improvements in behaviour and social interactions motivated adherence. It is imperative that parents receive accurate information about ADHD and it's treatments to address these concerns and empower them to make informed treatment decisions.

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Utilization of antihypertensive medication in elderly hospitalized patients

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Introduction. Hypertension is a common, manageable, chronic risk factor for cardiovascular disease associated with significant morbidity and mortality. Optimal hypertension management is important, yet it is estimated that a significant proportion of elderly patients remain poorly controlled despite wide availability of antihypertensive medications. Understanding the current patterns of antihypertensive utilization is essential for ensuring quality use of medicines and optimising clinical care in elderly hypertensive patients.

Aims. To identify patterns of antihypertensive medication use, including changes to treatment during hospitalisation, in elderly patients.

Methods. A retrospective, cross-sectional study of medical records for elderly patients (age ≥65 years) admitted to a large tertiary teaching hospital in NSW from January to December 2010 was conducted. Medical records were audited to determine the hypertension prevalence and antihypertensive medication use.

Results. Here we present the results for the first 117 patients (mean age: 80.7 years, range: 65.4-99.0, 62.4% female). More than half of the patients (62.4%, n=73) had a documented diagnosis of hypertension and on admission the most commonly prescribed antihypertensives were ACEIs (24.8%, n=18) followed by CCBs (22.7%), ARBs (19.1%), beta-blockers (16%) and diuretics (14%). During hospitalisation 45% (n=33) of patients experienced changes to their antihypertensive regimen. The main changes were cessation of antihypertensive medications, dose reductions or temporary addition of additional antihypertensive agents. The most common reasons documented for these changes were adverse drug reactions (ADRs) (42%, n=14), in particular renal injury and bradycardia, and sub-optimal blood pressure control (33%, n=11).

Discussion. The high prevalence of ADRs associated with antihypertensive medication use in found in this study adds to the challenges of optimal hypertension management in the elderly. Pharmacists need to take this into consideration when optimising blood pressure management during hospitalisation, and need to consider strategies to

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Using academic detailing to support nurses' knowledge and confidence around antipsychotic drugs in dementia

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Introduction. Antipsychotic agents are frequently prescribed for behavioural and psychiatric symptoms of dementia, despite having modest efficacy and possessing a potential to cause serious harm.
Aims. This project aimed to increase the knowledge and confidence that aged care nurses have about the use of antipsychotic agents in dementia.
Methods. 20 nurses working in five residential care homes in the Brisbane area participated in an academic detailing session about use of antipsychotic agents in dementia. The nurses' knowledge and confidence around the use of antipsychotic drugs in dementia was measured pre-and-post intervention with a multiple choice quiz and a survey. Certainty based assessment was used to assess nurses' knowledge regarding the topic and the confidence with which the nurses held this knowledge. The quiz was scored such that respondents that were more often correct with confidence scored higher than those that correct with low confidence or confidently incorrect. The primary assessment of the effectiveness of the academic detailing session was the median change in quiz score. Secondary endpoints included changes in the number of correct answers on the quiz and changes in survey score.
Results. 16 of the 20 nurses who received the education responded to the follow-up quiz and survey, a response rate of 80 %. The median quiz score increased from 9.5 points to 21.0 points ($p = 0.002$) on a scale from – 60 to + 30 points. The median number of correct answers on the same quiz increased from 7 to 9 out of 10 ($p = 0.0002$). Respondents reported a high degree of confidence in the survey before and after the academic detailing session.
Discussion. A targeted academic detailing session improved nurses' knowledge and confidence about the use of antipsychotic drugs in dementia. Most importantly, participants were more likely to be right and confident they were right.

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Interprofessional learning: impact on collaboration and attitudes towards health care teams.

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Introduction. Health care professionals (HCPs) in primary care a accustomed to working in isolate, hence, for this and many other reasons, collaboration rarely occurs. The Collaborative Asthma Management in the Community (CAMCOM) project involved the development, implementing and evaluating 3 models of interprofessional education on collaborative practice and patient health outcomes. This abstract focuses on the impact of CAMCOM on health care professional collaborative practice.
Aims. To compare the effect of three "interprofessional" educational interventions on attitudes towards collaboration and markers of interprofessional practice.
Methods. HCPs from three general practice networks were recruited into three groups (1, 2, and 3) receiving one of three models of inter professional education (i.e. joint setting group, online group and socio-cultural theory-based group, respectively). HCPs were then required to recruit and review patients with asthma five times over a six month period. Collaborative practice was evaluated through a series of process measure. Attitudes toward collaboration/health care teams was evaluated using the Attitudes Towards Health Care Team Scale (ATHCTS).
Results. A total of 37 pharmacists, 13 general practitioners and 2 practice nurses recruited 312 patients with asthma. No significant difference was detected in ATHCTS between Groups 1, 2 and 3 over time. Of the 945 patient completed only 5% were seen by both a GP and pharmacist (10% in Group 1, 11% in Group 2 and 3% in Group 3). Of these visits 81%, 94% and 37% were entered on the electronic patient log by HCPs from Groups 1,2 and 3 respectively.
Discussion. Achieving collaboration in primary care remains a challenge, despite the method of training, the availability of a model of practice and clinical support. Future research should involve the Pharmacy Practice Incentives, which can provide a mechanism of remuneration within the current health care environment.

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Perceived barriers to pharmaceutical services by clients with mobility, vision and hearing disabilities

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Introduction. Twenty per cent of the Australian population live with functional disabilities. Structural problems such as lack of wide doorways and ramps, communication difficulties and lack of provider knowledge about disability-related issues are barriers for people with disabilities to receive timely, high quality pharmaceutical services.
Aims. To investigate the perceived barriers of people with mobility, hearing and vision impairment in accessing pharmaceutical services and to determine whether these are different in non-disabled persons.
Methods. Self-administered surveys, available on paper and online, were collected from adults without a disability and from adults who have mobility, hearing or visual impairment from WA and other states in Australia. All participants took part in the study voluntarily; those with a disability were recruited through contacting various organisations and advertising the survey on disability-related internet websites. Data were analysed using the SPSS statistical software.
Results. 170 valid responses were identified for analysis (110 with disabilities and 60 non-disabled). Small writing on the label was the main barrier for the non-disabled (30%) and vision impaired (71.4%) groups. This was also a common barrier for the other two groups. The mobility disabled group (72.7%) had problems with a cluttered pharmacy, whereas the hearing disabled group (40.8%) felt uncomfortable with the way pharmacist communicated with them. Both the non-disabled and mobility disabled groups reported physical barriers such as small space and high counter level, while the vision and hearing disabled groups identified communication barriers such as the lack of suitable information formats as well as modes of interaction as major impediments. Only 76% of the whole group indicated that they were confident about their medicines when leaving the pharmacy.
Discussion. The study has identified areas for improvement in the provision of pharmacy service at primary care settings not only to clients with disabilities, but also the non-disabled clients.

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ASCIA Anaphylaxis Training for Pharmacists

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Introduction. Maintaining knowledge in anaphylaxis management may save lives. The Australasian Society of Clinical Immunology and Allergy (ASCIA) provides lecture-based and e-training anaphylaxis courses for Australian health professionals, school and childcare staff.
Aim: To assess the effectiveness of ASCIA anaphylaxis lectures for pharmacists.
Methods. Approved ASCIA members presented the ASCIA lectures. Australian pharmacists and pharmacy students who attended lectures and agreed to participate were included. Effectiveness (gain and retention of knowledge) was measured using a twelve-item test administered pre, post, three and seven months after lecture completion. Mean pre and post scores were compared to determine knowledge gain. Mean scores pre and three, and pre and seven months after course completion were compared to determine retention. Frequencies were used to determine the pass rate for each test (scores> 9/12 (75%)).
Results. Pre and post-tests were completed by 152 pharmacists and 62 students, with 89 pharmacists (59%), and 45 students (73%) completing 3-month tests. Seventy-eight pharmacists (52%) and 34 students (55%) completed 7-month tests. Mean knowledge gain was 4.3 points ($p<0.001$). Mean retention at 3 and 7 months was 2.5 points ($p<0.001$) and 2.9 points ($p<0.001$) respectively, with retention at 7 months being significantly greater than at 3 months ($p<0.001$). Mean gain and retention was significantly greater for students compared to pharmacists (gain: 5.7 vs 3.7 points; retention-3 months 3.8 vs 1.9; retention-7 months 4.2 vs 2.4), all $p<0.001$. More pharmacists than students achieved a pass at every test: 97% vs 85%; 60% vs 53% and 80% vs 62% scored >9/12 for post, 3 and 7-month tests respectively.
Discussion. ASCIA anaphylaxis lectures for pharmacists significantly increased short and long-term knowledge. Pharmacists consistently achieved higher pass rates than students, with the majority at seven months retaining sufficient knowledge to achieve a pass.

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Risk factors for chlamydia: A survey of pharmacy-based emergency contraception consumers in Australia,

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Introduction. In 2005, the Australian federal government stated that chlamydia screening programs should target the following: sexually active people aged 15-29 years, those that have experienced inconsistent use of barrier contraception, those with multiple sexual partners, and those with a history of a sexually transmitted infection.
Aims. To determine the prevalence of the above mentioned risk factors in pharmacy-based emergency contraception (EC) consumers; evaluate their pharmacy experience; and determine if they would be willing to accept a chlamydia test from the pharmacy in Western Australia.
Methods. A survey for women to complete after their EC consultation was developed from themes indentified in a literature search. 24 pharmacies participated in this study.
Results. From 113 surveys completed, 85% were 16-29 years of age and all (100%) women had inconsistent use of barrier contraception. 94% of the women had at least two, and 47% had at least 3 out of the 4 risk factors. 70% of women found pharmacy very easy/easy to access a pharmacy and felt very comfortable/comfortable discussing EC with the pharmacist. Most (72%) said they would accept a chlamydia test from a pharmacy.
Discussion. Women requesting EC from a community pharmacy are at high risk of chlamydia. Yet there is no mechanism by which pharmacists can request a chlamydia test in Australia. There is an urgent need to re-orientate health service so that pharmacists can offer women requesting EC a chlamydia test.

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Off-label and unlicensed prescribing in a Western Australian paediatric population

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Introduction. Unlicensed and off-label prescribing in paediatrics is a global phenomenon due to a lack of adequate registrations of paediatric drugs and formulations. Data on the extent of off-label and unlicensed prescribing in paediatrics in Australia is limited.
Aims. To evaluate the extent of off-label and unlicensed prescribing trends in a large paediatric hospital in Western Australia.
Methods. 1037 randomly-selected medication chart records from a single year (2008) from Princess Margaret Hospital for Children (PMH) were analysed for prescribing trends in paediatric emergency department admissions, outpatients and inpatients. Relevant patient data, prescribing details, diagnosis and adverse effects, were collected. Drugs were classified according to the ATC code. Standard statistical tests were applied.
Results. Most records (n =403; 39%) were from the Emergency Department; 37% as outpatients (n = 382) and 24% as inpatients (n = 253). A majority were males (58% in ED, 55% outpatients, 65% inpatients). There were 2660 drugs prescribed to 700 patients with inpatients administered significantly more drugs per person than emergency outpatients ($p < 0.0001$). Of the 253 inpatients, 154 males (79%) and 63 females (74%) received one or more off-label or unlicensed drug ($p < 0.0001$). The overall extent of off-label or unlicensed prescribing in all settings was 28%, with the greatest number administered to inpatients aged 2 to 5 years (mean 1.9). The most common ATC categories with off-label prescribing included the nervous system (44%), alimentary tract (20%) and anti-infectives (14%). Drugs commonly prescribed off-label included ondansetron, Painstop Day, salbutamol, oxycodone, paracetamol, midazolam, fentanyl, amoxycillin, flucloxacillin and ticarcillin with clavulanic acid.
Discussion. Off-label prescribing was common at PMH, with inpatients more likely to receive them than outpatients or emergency admissions. Although off-label prescribing is widespread, a paediatric formulary is essential to provide up-to-date and evidence based information on their uses.

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Medicines and their management among the older-aged living independently in leasehold retirement villages

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Introduction. Half of the older-aged, living in rental retirement villages, are nonadherent, or at risk of being nonadherent. They had a good knowledge of their illnesses for about half of their prescribed medicines, whereas those older-aged living in freehold rental retirement villages were much more adherent and had a better knowledge of their medicines/illnesses (Doggrell & Kairuz, 2012). Most of the older-aged that live in retirement villages live in leasehold villages. Unfortunately, initially we were unable to recruit enough participants from leasehold villages to assess their management of medicines.

Aim. The aim was to recruit participants from leasehold retirement villages, and compare their adherence and knowledge of medicines to those in rental and freehold retirement villages.

Method. Semi-structured interviews with the researchers rating their perception of the adherence, as described previously (Doggrell & Kairuz, 2012).

Results. The mean age of the participants at the leasehold retirement village was 83 years ±2 (n=22). Our perception was that 55% of the older-aged were fully adherent and unlikely to have problems in the next 6-12 months, whereas 41% were presently fully adherent but at risk of not being so in the future. The participants were taking 9.8±1 medicines each, with the commonest medicines being cardiovascular, followed by gastrointestinal and respiratory medicines. With regard to relating medicines to illnesses, the participants were good at this for 58% of medicines, and only had some or no knowledge of the medical use of their other medicines.

Discussion. The older-aged in leasehold villages were intermediary between the predominantly fully adherent in the freehold villages and the less adhering older-aged in the rental villages. Like the residents of the rental retirement village, many of the participants from the leasehold village did not have a good understanding of which illnesses their medicines were being prescribed for.

Doggrell SA, Kairuz T (2012) Journal of Pharmacy Practice and Research, 42:208-12.

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The role of a medication incident reporting system in monitoring and signalling medication safety risks in primary care

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Introduction. One objective of the National Medicines Policy is to ensure timely and uninterrupted access to medicines through efficient distribution networks. Manufacturing problems can disrupt medicine supply and create quality and safety concerns for patients and health-care providers (HCPs). A medication incident (MI) reporting system may play surveillance and signalling roles by detecting the impact of and response to disruptions to medicine supply.

Aims. To identify an incident cluster for disruption to medicine supply from incident reporting data and reveal contributing factors and preventive strategies.

Method. Thirty community pharmacies in Sydney participated in a 28-month incident reporting study (QUMwatch) providing data on the nature of MIs in primary care. Data classification, management and analysis utilised AIMS® software. Process classifications and narrative text was searched to identify incidents associated with supply.

Results. 952 MIs were reported and 395 were analysed. MIs occurred during all stages of the medication use process. A cluster of spontaneous MI reports, related to disrupted supply for extended-release metformin products, signalled safety concerns including patient confusion, treatment interruption, ineffective communication from manufacturers and deficient processes and tools to advise and support HCPs and patients in selecting alternative therapies.

Discussion. A MI reporting system can identify risks, such as medication supply disruptions, and their underlying causes and generate strategies to prevent or moderate recurrence of emerging risks. A multidisciplinary national reporting system may facilitate large-scale trend analyses across a number of real-world situations to manage risks from medicines use.

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The perceived efficacy of non-prescription medications used by women who experience PMS

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Introduction. Premenstrual syndrome (PMS) is a multi-factorial condition which includes a wide range of symptoms and affects women of reproductive age. PMS is often self-diagnosed and treated by women. Various pharmaceutical preparations are available for the treatment of PMS, with varying degrees of clinical evidence. However, consumers' choice is not always based on clinical evidence.
Aims. This study aims to examine the consumers' perceived efficacy of non-prescription products marketed for the relief of PMS and period pain, which include vitex, evening primrose oil [EPO], ibuprofen, mefenamic acid, and naproxen.
Methods. The study utilises a 10 question survey questionnaire. Participants were recruited from 9 community pharmacies, over 3-6 weeks. Data analysis was performed using the Qualtrics Survey Software.
Results. A total of 47 completed surveys were returned to the research team. The characteristics of the menstrual cycles of the participants were comparable to the published literature, regarding length of menstrual cycle, duration of menstrual bleeding, and nature of PMS symptoms. Among the participants the most commonly used non-prescription products were the non-steroidal anti-inflammatory drugs (87%). Other products being used were EPO (13%) and vitex (4%). The greatest efficacy was reported from subjects who had been using EPO followed by ibuprofen and naproxen.
Discussion. The study identifies that women's perception of the efficacy of these products does not correspond to currently available clinical data, in which vitex is the only product that has clinically proven efficacy and safety for PMS and EPO has no clinical data to support its efficacy. Future studies are required to examine the safe and effective use of non-prescription products in PMS.

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Identification of medication errors amongst healthcare providers and academics in Denpasar Bali

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Introduction. The Joint Commission on Accreditation of Healthcare Organizations in the United Sates has identified the prevention of adverse drug events, which include medication error, as a major health initiative. The ability to identify medication errors is crucial for healthcare practitioners in order to ensure the quality and safe use of medications.
Aims. To compare the ability to identify medication error amongst healthcare providers (physician, nurses and pharmacist) at Sanglah Hospital and medical, nursing and pharmacy academics at Udayana University in Denpasar, Bali.
Methods. Healthcare providers at Sanglah Hospital and academics at Udayana University were randomly selected to participate in the study. Participants received six case vignettes. Each case had a set of standard questions on identifying patient's problem, type of errors, reasons for errors, profession responsible for the errors, what should be done to prevent recurrence, and level of severity of these errors. The case vignettes were translated into Bahasa and were piloted to potential participants. Simple descriptive statistics were used to summarise the data, and a regression model were used to compare the accuracy of answers between the different professions.
Results. 315 of 550 (57.3%) participants returned the survey which consisted of 23 physicians, 200 nurses, and 17 pharmacists at the hospital and 47 medical, 10 nursing, and 18 pharmacy academics at the university. Accuracy of responses was higher for pharmacists with the odds ratio of 1.63 (95% CI: 1.29 to 2.06) compared to physicians and nurses. Accuracy of response was also higher for pharmacy academics with odds ratio of 1.70 (95% CI: 1.18 to 2.35) compared to medical and nursing academics. Respondents largely agreed on the profession responsible for the errors.
Conclusion. Pharmacy academics and practitioners identified medication errors more accurately compared to both nursing and physician academics and practitioners.

Joint Commision (2010) Root cause analysis in healthcare: tools and techniques, ed Richard JC. pp 1-21, USA, Joint Commission Resources

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Assessment of Chronic Pain in the Community

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Introduction. Chronic pain is a major public health problem which costs Australia an estimated 5.1 billion dollars per year in lost productivity alone. Due to its subjective nature, assessing the adequacy of chronic pain management is complex and there is currently no validated tool that assesses chronic pain management in community-dwelling individuals.
Aims. To investigate the adequacy of management of community-dwelling people with chronic pain.
Methods. A cross-sectional quantitative study design was used. Pharmacies from across Australia distributed questionnaires to people dispensed a prescription for an oral or transdermal analgesic. Data analysis was performed using SPSS. Multivariate analysis of variance was used to determine the optimal cutpoint scheme which would differentiate mild, moderate and severe pain. This was based on reported activities and emotions. The relationship between participants having mild, moderate or severe pain and variables including age, gender and socio-economic status was also assessed.
Results and Discussion. Of the 200 respondents 61% were using strong opioids and 70% were using non-medication methods to treat their pain. Average pain in the past week was reported on a scale from 0-10 (M=5.55, SD=2.13). The cutpoint scheme that best discriminated between mild, moderate and severe pain was 3 and 6. According to this over three quarters of the sample reported moderate or severe pain which may indicate inadequate pain management. Gender and socio-economic status were not related to pain level but age was. Younger people were more likely to report high pain levels which may be because older people have lived with their chronic pain for a longer period of time and because they report lower affective qualities of pain and lower life interference scores. People reporting average pain in the past week on a 0-10 scale can be classified as having mild (0-3), moderate (>3-6) or severe pain (>6-10). People of different ages report different levels of pain with younger people reporting more severe pain.

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A taste of your own medicine: prevalence of symptoms and self-medication in the community

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Introduction. Understanding the prevalence of symptoms and the responses people make to these symptoms, including self-medication, is key to encouraging optimal use of medicines. However, most research either engages with people who are sick enough to have sought advice from a healthcare professional, or asks people to try to recall past illness and treatment. These will however miss a substantial proportion of self-medication, where no advice is sought, or the symptoms and treatment are not recalled, due to their minor or passing nature.
Aims. To gain insight into the prevalence of symptom experience and self-medication in a community-living population, using a prospective cohort design.
Methods. Random sampling from the Dunedin White Pages was used to recruit participants aged 18-65. After filling out an initial questionnaire, participants were contacted on daily basis via email or text message for 30 days, asking if they had experienced symptoms in the last 24 hours. Had symptoms been experienced, participants filled out a longer online questionnaire about their symptoms, whether they had self-medicated, and if they had consulted a healthcare professional.
Results. 154 participants were recruited, with 152 completing 30 days. Over the 30 day period 83.5% reported at least one symptom, with headache (60.6%) being the most prevalent. Using a medicine already in the house was the most common response on any symptomatic day (40.8%) with only a small proportion of participants choosing to seek professional medical help. Despite participants rating pharmacists as the best choice for treating minor symptoms, doctors (2.6%) were more commonly consulted than pharmacists (1.2%).
Discussion. Symptoms were experienced frequently by participants, many of which would be unlikely to be recalled in a retrospective design. Self-medication was the most common response, with evidence of non-optimal medicines use, suggesting the need for strategies to improve self-medication and engagement with pharmacists.

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The effect of weak English skills on academic performance, and the effectiveness of English language screening and remedial help for pharmacy students

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Introduction. English language proficiency is required for registration as a pharmacist in Australasia. Thus, educational institutions often screen to detect pharmacy students with weak English. The impact of weaker language skills, and the effectiveness of screening, is difficult to determine if students are selected on the basis of English language proficiency or a proxy (such as an interview). However, while pharmacy students at Otago are screened for English language prior to entry, they are selected solely based on grade average.
Aims. To examine the effect of weak English on performance in pharmacy education, and also the effectiveness of English language screening and remedial help.
Methods. A retrospective cohort study, comprising all students entering the programme directly from a common health science first year (HSFY) in 2007-2009. Relationships were examined between results from an HSFY screening test, subsequent screening tests in the pharmacy programme, and their academic grades and progress.
Results. Poor performance on English screening tests had a lasting impact on academic performance. Failing the HSFY and second year screening tests both predicted lower grades (*B*s>-4.1, *p*s<.01), a greater likelihood of failing one or more papers (Odds ratio 2.9, $p<.01$), and a greater likelihood of having to repeat a year of the pharmacy programme (Odds ratio 3.0, $p<.05$), controlling for academic performance at entry. Almost all students who failed the HSFY test also failed a second screening test a year later, despite having successfully passed a semester long remedial course in between the tests.
Discussion. Difficulties with English have a pronounced effect on students' performance in pharmacy education. English screening tests appear to be effective in identifying students with poorer English skills, but it may be difficult for students to improve their language skills while studying full time. This presents an ongoing challenge to pharmacy educators.

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The impact of the rescheduling of combination analgesics containing codeine on the practice of pharmacists

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Introduction. On the 1st May 2010 combination analgesics containing codeine (CACC) changed from Schedule 2 to Schedule 3 meaning that the involvement of a pharmacist is now involved in all sales.
Aims. To explore how the rescheduling of CACC has impacted on the practice of community pharmacists.
Methods. A descriptive qualitative design was used, with data collected via face-to-face semi-structured interviews that were recorded and transcribed verbatim. The data was analysed thematically via open, axial and selective coding.
Results. From the eleven pharmacists interviewed, it was found that pharmacists monitor the supply of CACC by recoding sales and will intervene when they feel that the medication is being overused. Pharmacists perceived there to be a number of challenges surrounding the provision of CACC. These relate to inconsistent procedures between pharmacies, being unaware of CACC supply from other pharmacies and how to assist dependent people.
Discussion. The extent to which pharmacists record sales varies with some recording all sales, whilst others selectively record for certain patients or products. This different approach can lead to patients feeling singled out or cases of overuse not being detected. Pharmacists also felt that inconsistent procedures at different pharmacies are leading to customer misunderstandings. Respondents expressed the desire for a national monitoring system so that they would be aware of patients purchasing CACC from other pharmacies, which is not currently possible because their records are limited to their own pharmacy. Strategies used by pharmacists when they detect overuse of CACC are educating patients about side effects, recommending alternative treatments, refusing sales and referring to the doctor. However, respondents lacked confidence to raise the issue of suspected misuse and codeine dependence and were unsure of where to send dependent people for help. Investigation into more effective ways of identifying and intervening in codeine dependence is required.

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Commercial influences on community pharmacist recommendations – impact of the Extended and Accelerated Price Disclosure

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Introduction. Community pharmacy faces an inherent conflict between fulfilling professional responsibilities and maintaining a profitable business. We have previously shown that generic substitution by pharmacists was influenced by commercial factors including higher profitability. However, fulfillment of legal and professional requirements with these substitutions was not fully met. The first Main Disclosure Cycle of the Extended and Accelerated Price Disclosure (EAPD) occurred on 1 April 2012 and resulted in a 10-73% price reduction across a range of prescription medicines.
Aims. To examine if the pattern of generic substitution of prescription medicines is affected by the EAPD reduction in margin.
Methods. Ten community pharmacies around Brisbane were recruited to provide a range of business types and demographic settings. Observational studies were carried out after 1 April 2012 over six three-hour session and all prescription transactions were recorded. These results were analyzed to determine generic substitution rates and concordance with professional requirements, and also compared with our historical data which were collected before EAPD.
Results. It appears that the rate of generic substitution of prescription medications was increased across all study pharmacies. However, there appears to be an increase in the number of transactions that were not handled to meet the professional and legal requirements. Further data collection and analysis are underway.
Discussion. The increase in generic substitution appears to be a response to boost profitability after EAPD. This should in turn drive generic substitution and reduce government cost - an aim of EAPD. The decline in professional standards is of concern as increased substitution will require more explanation to prevent medication misadventure and provide QUM improvements to accompany the financial benefits of EAPD.

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Concomitant use of alcohol and sedative-hypnotics in middle and older aged people: a systematic review

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Introduction. Interactions between alcohol and sedative-hypnotics may result in adverse events. Patterns of alcohol drinking and sedative-hypnotic drug use differ between countries.
Aim. To conduct a systematic review on the prevalence of concomitant alcohol and sedative-hypnotic use among middle-aged and older persons.
Methods. MEDLINE, EMBASE and PsycINFO (January 1990-present) were searched using Medical Subject Headings and keywords. Population-based studies reporting the quantity of alcohol drinking, prevalence of sedative-hypnotic use, and in which the mean age of participants was ≥40 years were included in the review.
Results. Five population-based studies conducted in North America, ten in Europe and one in Australia were included in the review. Up to 88% of men and 79% of women who used sedative-hypnotics also consumed alcohol. Up to 28% of those who consumed alcohol were concomitant users of sedative-hypnotics. Middle-aged people consumed higher quantities of alcohol and exhibited more risky drinking patterns, including binge drinking and heavy drinking, than older persons. In contrast, sedative-hypnotic use was more prevalent among older than middle-aged persons.
Discussion. Our review identified a higher prevalence of alcohol consumption among middle-aged than older persons. Middle-aged persons may experience harm from alcohol/sedative-hypnotic drug interactions due to risky drinking behavior. Older persons have a higher prevalence of sedative-hypnotic use and may be more susceptible to addictive central nervous system effects than younger persons due to physiologic changes in psychotropic drug and alcohol metabolism. Clinicians should consider patients' alcohol consumption patterns before prescribing sedative-hypnotic drugs.

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The Medwise Model – is it working in the Bay of Plenty?

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Introduction**:** Medwise has provided a District Health Board (DHB) funded pharmacist support service that has enabled medicines management, support and education for high risk patients in the Bay of Plenty since 2008. There is very little New Zealand data about the range and extent of services provided for this group of patients.
Aim: Investigate the origin of referral and demographics of patients referred to the Medwise service in the Bay of Plenty.
Method: Interventions carried out by Medwise pharmacists were analysed to determine the scope and range of services provided using a retrospective cohort study of Medwise records from June 2008 to November 2011. The only criterion required for a patient to enter the service was that they had potential or existing medication-related problems.
Results: Data from 297 patients were analysed (mean age 74 years, 49% male, 26% Maori), of which 38% were referred because of poor adherence or confusion about their medicines. The categorisation of interventions (n=101) showed that pharmacist recommendations to alter medication dose, interval or frequency, or review the appropriateness of a medicine had a low implementation rate (<15%). Cardiovascular medicines required the most frequent interventions (35%). Only 20% of the patients referred were due to issues surrounding polypharmacy or a medication review. 36 (65%) of those referred for support with adherence and education resulted in a therapeutic intervention request. 45% of all cases took from 1 to 3 hours to complete.
Discussion: Medwise is a successful DHB-funded service that patients are being appropriately referred to. The introduction of pharmacist prescribing in New Zealand will allow pharmacists to provide individualised medicines management services to patients such as prescribing medicines and increasing the implementation of clinically appropriate interventions.

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Timing of the Drug Administration in Clinical Practice in Australia

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Introduction. Timing of drug administration is important for health care professional and pharmacists. The concept of chronotherapy is an emerging field in healthcare, which deals with finding the optimal time of drug administration. This review scopes the evidence of chronotherapy in current clinical practice.
Aims. To find and evaluate the evidence of chronotherapy in top 20 (by volume) Pharmaceutical Benefit Scheme (PBS) drugs in Australia and to identify how well this information is considered in clinical practice though Monthly Index of Medical Specialties (MIMS).
Methods. The search was conducted in MEDLINE and IPA using the keywords “Drug Chronotherapy”, “Drug administration Schedule”, “Administartion Time Dependent effects”, “Circadian Rhythms”, “Chronopharmacology”, “Chronopharmacokinetics”, “Chronopharmacodynamics”, “Morning and Evening”, “Morning and Bedtime”, “Morning and Night time” and their combination which was later filtered with top 20 PBS drugs sold in Australia. Articles were limited to English language, humans, year (1990-April 2012) and Clinical Trials.
Results. Our search revealed a total of 770 articles, of which 12 articles were selected for review. The evidence for chronotherapy that was tested in these 12 studies were Atorvastatin (n=2), Rosuvastatin (n=1),Simvastatin (n=3), Perindopril (n=1), Pantoprazole (n=1), Irbesartan (n=1), Atenolol (n=1),Rabeprazole (n=1) and Ramipril (n=1). The most common study design utilized in these studies was the Randomised Control Trial (RCT) (n=11). The timing of drug administration is defined for Simvastatin (evening) and Perindopril (morning) in MIMS.
Discussion. The study presents the scope of chronotherapy in clinical practice. Our analysis revealed three categories of drugs. (1) Chronotherapeutic drugs used in clinical practice, (2) The potential chronotherapeutic drugs not used in clinical practice and (3) The drugs that has chronotherapeutic potential but not researched. There is a need to bring awareness of chronotherapeutic drugs in clinical practice for health care professionals.