Background: In patients with type 2 diabetes (T2DM) fixed-dose antihyperglycaemic combinations (FDCs) may provide complementary efficacy, reduce tablet burden, and improve compliance. The aim of this study was to assess the bioequivalence and tolerability of 2 strengths of dapagliflozin (DAPA)/metformin extended-release (MET-XR) FDCs versus their individual components (ICs) in healthy subjects.
Material and Methods: This open-label, randomised, 2-way crossover, 4-arm study was conducted in 141 healthy adult Brazilian subjects. Two oral doses (5 mg DAPA/500 mg MET-XR and 10 mg DAPA/1000 mg MET-XR) were evaluated in fed and fasted states.
Results: Under fed and fasting conditions the 5 mg DAPA/500 mg MET-XR FDC was bioequivalent to its ICs (Table). The 10 mg DAPA/1000 mg MET-XR FDC was bioequivalent to its ICs only in fed patients. C_{max} for metformin was not bioequivalent to its ICs (upper 95% CI outside 80%–125%) in fasted patients; this small increase was not considered clinically meaningful as metformin is recommended to be administered with food. The safety and tolerability of the FDCs were generally similar to their ICs; no serious adverse events were reported.
Conclusions: Both DAPA/MET-XR FDCs were bioequivalent to their ICs, except 10mg DAPA/1000mg MET-XR in fasted patients, supporting their use in patients with T2DM.

		Parameter	Geometric mean point estimate of FDC/IC (%)	CI (90%) for the point estimate
5 mg DAPA/500 mg MET-XR				
Arm-1 (n = 34) asted	Dapagliflozin	C_{max}	104.7	(96.3; 113.7)
		$AUC_{0\text{-}inf}$	101.1	(98.0; 104.2)
	Metformin	C_{max}	96.7	(87.1; 107.5)
		$AUC_{0\text{-}inf}$	101.7	(93.3; 110.8)
Arm-2 (n = 29) Fed	Dapagliflozin	C_{max}	96.6	(88.0; 106.0)
		$AUC_{0\text{-}inf}$	102.0	(98.9; 105.2)
	Metformin	C_{max}	100.9	(95.1; 107.0)
		$AUC_{0\text{-}inf}$	104.6	(97.3; 112.4)
10 mg DAPA/1000 mg MET-XR				
Arm-3 (n = 34) Fasted	Dapagliflozin	C_{max}	103.7	(96.2; 111.7)
		$AUC_{0\text{-}inf}$	102.7	(100.7; 104.8)
	Metformin	C_{max}	118.3	(109.8; 127.5)
		$AUC_{0\text{-}inf}$	112.6	(104.8; 120.9)
Arm-4 (n = 32) Fed	Dapagliflozin	C_{max}	91.9	(80.9; 104.4)
		$AUC_{0\text{-}inf}$	99.1	(97.0; 101.3)
	Metformin	C_{max}	107.1	(102.6; 111.8)
		$AUC_{0\text{-}inf}$	98.6	(93.2; 104.3)

3D PHOTOGRAPHY FOR SKIN LESION QUANTIFICATION

G. Hogendoorn[1]; C. Lemoine[1,2]; R. Rissmann[1,2]; and J. Burggraaf[1,2]
[1]*Centre for Human Drug Research, Leiden, The Netherlands; and* [2]*Leiden University, Leiden, The Netherlands*

Introduction: Reliable methods to quantify skin lesions are critical for the evaluation of disease severity and assessment of therapeutic response. In dermatological trials often two dimensional digital photography is utilized which has inherent disadvantages. It appears that high-resolution three-dimensional (3D) imaging may offer many advantages such as offline 3D visualization and automatic picture segmentation resulting in an objective and detailed skin lesion characterization. At present this technique is not optimally technical and analytical validated which is a pre-requisite for clinical application.
Material and Methods: In this study we investigated the performance and clinical use of the 3D skin-imaging LifeViz™ system (Quantificare, Sophia Antipolis, France) in conjunction with the DermaPix Software. The validation of the LifeViz Micro was conducted with four trained operators that captured a synthetic phantom object on three different skin backgrounds at four time points during a period of one week.
Results: Coefficient of variations for volume of the 3D system were 1.0%, 2.6% and 1.4% for inter-operator, skin background and inter-day variability, respectively. The overall precision of the system was 2.7% for volume, 1.6% for diameter and 4.1% for height. In order to determine accuracy of the system, a ruler was photographed and a mean error of 0.3% (range 0.0-0.8%) was observed. Preliminary data on cutaneous lesions also show low inter-observer variability and accurate images.
Conclusions: This validation study demonstrates that this novel 3D-imaging system is precise and objectively quantifies a phantom object representing a skin lesion. The results support clinical use of this technology enabling high-resolution computation. Also the accuracy results are promising, but needs to be extended with accuracy assessment of absolute measurements. The preliminary clinical data suggest that application of this non-invasive imaging technique is suitable to quantitatively measure characteristics of cutaneous lesions and may be a promising tool in clinical trials.

THERAPY ADHERENCE IN ELDERLY OF NORTHERN PORTUGAL

I.C. Pinto[1,3]; F. Pereira[2]; and R. Mateos-Campos[3,4]
[1]*Center for Research and Intervention in the Elderly, Health School of Polytechnic Institute of Bragança, Portugal* (isabel.pinto@ipb.pt); [2]*Center for Research and Intervention in the Elderly, Polytechnic Institute of Bragança, Portugal* (fpereira@ipb.pt); [3]*School of Pharmacy, University of Salamanca, Spain; and* [4]*INESPO - Innovation Network Spain-Portugal* (rmateos@usal.es)

Introduction: The elderly population has been growing significantly, leading to an increased prevalence of chronic diseases and consequent taking medication. The complex therapies of elderly can lead to therapy non-adherence, increasing several health risks.
Aim: This study aimed to estimate the prevalence of therapy adherence and associated factors.
Material and Methods: This cross-sectional study was based on a questionnaire, with MAT scale (measure of adherence to therapy) validated for the Portuguese population (Lima, 2001) based on the Morisky scale, applied to 52 elderly (≥65 years) from northern Portugal. To assess therapy adherence, those whose average adherence levels were ≥5, were called adherent. It was used descriptive statistics. The level of association between categories of variables was studied through the adjusted residuals (AdR) and the relationship between adherence to the therapeutic and the number of medications taken per day was studied using the Mann-Whitney U test, with a significance level of 5%. The study was approved by Ethics Committee.
Results: The sample consisted mainly of males elderly (61.5% vs. 38.5%), aged between 67 and 98 years (mean 82.71), and while 48.1% was between 75–84 years old. The participants shows high therapy adherence (96.2%). The non-adherent elderly are related to self-medication (AdR=4.3), with the high level of cholesterol (AdR=2.9) and chronic pain (AdR=2.9). The non-adherent elderly seem tend to take more drugs per day, although not statistically significant ($P = 0.063$).
Conclusions: This study shows that a large prevalence of elderly adhered to the therapy prescribed. Self-medication, having high cholesterol and chronic pain and higher number of different drugs per day seem related to non-adherence.
Key words: Elderly, Therapy adherence, Therapy non-adherence.

A LIMITED NUMBER OF PRESCRIBED DRUGS ACCOUNT FOR THE MAJORITY OF CLINICALLY RELEVANT DRUG INTERACTIONS

J. Holm[1,2]; B. Eiermann[1]; E. Eliasson[1,2]; and B. Mannheimer[1,3]
[1]Karolinska Institutet, Stockholm, Sweden; [2]Karolinska University Hospital, Stockholm, Sweden; and [3]Södersjukhuset, Stockholm, Sweden

Introduction: Drug-drug interactions constitute a predictable and in many cases avoidable cause of adverse drug reactions and therapeutic failure. We conducted a register-based study to investigate the prevalence of prescribed combinations of interacting drugs in the whole Swedish population (Holm et al. Eur J Clin Pharmacol. 2014).
Material and Methods: A retrospective, cross-sectional register study was conducted, covering four months in 2010. Data from the Prescribed Drug Register on all dispensed drug prescriptions in Swedish pharmacies from January 1 to April 30 were linked to the drug-drug interaction database SFINX. The analysis focused on drug interactions classified in the database as clinically relevant that can be handled, e.g. by dose adjustments (C-interactions), and clinically relevant interactions that should be avoided (D-interactions). Interactions were categorized according to clinical consequence and drug type and prevalences of interacting drug combinations were described. The study was approved by the Regional Ethics Committee.
Results: About half of the population were dispensed at least one drug prescription. Mean (SD) number of dispensed drugs was 3.8 (3.4). About 2.5 million potentially interacting drug combinations were identified in the study population of 9.3 million people. Among detected interactions 38% were classified as C-interactions and 3.8% as D-interactions. About half of all C- and D-interactions were combinations of drugs with potential to cause therapeutic failure. The 15 most prevalent combinations accounted for 80% of D-interactions. The 10 most prevalent individual drugs were involved in 94% of all D-interactions.
Conclusions: A limited number of drugs and a few specific drug combinations account for the majority of D-interactions, i.e. clinically relevant interactions that should be avoided, in Sweden. About half of interacting drug combinations among C- and D-interactions potentially leads to treatment failure.

CHARACTERIZATION OF URACIL CATABOLISM VARIABILITY IN HEALTHY VOLUNTEERS

D. Kummer[1,2]; B. Rindlisbacher[1]; S. Fontana[3]; J. Sistonen[1]; U. Amstutz[1]; and C. Largiadèr[1]
[1]Institute of Clinical Chemistry, Bern University Hospital, and University of Bern, Bern, Switzerland; [2]Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland; and [3]Regional Blood Transfusion Service of the Swiss Red Cross, Bern, Switzerland

Uracil catabolism is crucial for the pharmacokinetics of the chemotherapeutic 5-fluorouracil (5-FU) since 5-FU is degraded by the same pathway. Decreased activity of the first catabolizing enzyme, dihydropyrimidine dehydrogenase (DPD), is a major predictor of 5-FU toxicity with known risk variants in the DPD gene (*DPYD*) accounting for ~30% of toxicities. However, not all toxicity cases can be explained by *DPYD* risk variants. To date, the phenotypic variability in the catabolism downstream of DPD by dihydropyrimidinase (DHP) and β-ureidopropionase (bUP), potentially contributing to 5-FU toxicity, has not been investigated. Thus, we aimed to characterize the baseline phenotypic variability of endogenous metabolites and metabolic ratios of 5-FU catabolism enzymes and to correlate the phenotype with genetic variation in the DHP and bUP genes (*DPYS* and *UPB1*).
Material and Methods: Three variants in *DPYS* and *UPB1* previously associated with 5-FU toxicity were genotyped in 320 healthy volunteers and their plasma uracil, dihydrouracil (UH_2), β-ureidopropionic acid (UPA), and β-alanine (BAL) concentrations were determined by LC-MS/MS.
Results and Conclusions: High inter-individual variability in all metabolic ratios was observed. Sex-dependent differences were detected at each enzymatic step in the uracil catabolism pathway, with lower metabolite levels ($P \leq 0.007$) in women. Moreover, lower UPA/UH_2 ratios ($P < 0.001$) were observed in women, suggesting that reduced 5-Fluoro-UH_2 catabolism may contribute to higher fluoropyrimidine toxicity rates observed in females. Furthermore, volunteers carrying *DPYS* variant c.265-58T>C had lower UH_2 plasma levels ($P = 0.033$) and higher UPA/UH_2 ratios ($P = 0.036$) and carriers of the *UPB1* variant c.1-80C>G showed lower BAL plasma levels ($P = 0.004$). These initial results are in agreement with the previously observed reduced fluoropyrimidine toxicity in c.265-58C carriers and increased toxicity in carriers of c.1-80G, indicating a possible functional effect related to these variants.

POLYPHARMACY AND POTENTIALLY INAPPROPRIATE MEDICATION IN ELDERLY OF NORTHERN PORTUGAL

I.C. Pinto[1,3]; F. Pereira[2]; and R. Mateos-Campos[3,4]
[1]Center for Research and Intervention in the Elderly, Health School of Polytechnic Institute of Bragança, Portugal (isabel.pinto@ipb.pt); *[2]Center for Research and Intervention in the Elderly, Polytechnic Institute of Bragança, Portugal* (fpereira@ipb.pt); *[3]School of Pharmacy, University of Salamanca, Spain; and [4]INESPO - Innovation Network Spain-Portugal* (rmateos@usal.es)

Introduction: The growing aging of population and increasing prevalence of chronic diseases require the simultaneous use of drugs, lead to the issue of polypharmacy and potentially interactions and inappropriate use.
Aim: To characterize polymedicated elderly and related factors, identify potentially interactions and inappropriate medication in elderly.
Material and Methods: This cross-sectional study was based on a questionnaire applied to 69 elderly (≥65 years) from northern Portugal. It was considered as polymedicated seniors taking ≥5 drugs. Beers list and the Delafuente classification were used to evaluate the therapeutic and possible interactions. It was used descriptive statistics and a model of binary regression, with a significance of 5%. The study was approved by Ethics Committee.
Results: The sample consisted mainly of males (53.6% vs. 46.4%), aged between 66 and 99 years (mean 82.01), while 65.2% have more than 80 years. However, most elderly are not polymedicated (58%), on average 4.61 different drugs are administered per day (maximum=19), antihypertensives (36.2%) and antacids (30.04%) are the most prescribed. Hypertension and depression increase the risk of polymedication eightfold ($P = 0.004$) and fivefold ($P = 0.011$) respectively. Female gender seems increase the risk of polypharmacy threefold, although not statistically significant ($P = 0.102$), and regarding age, the older age group (>85 years) seems reduces the risk of polypharmacy in 0.6 fold, but also not statistically significant. According with Delafuente classification, 1.4% of elderly has potentially drug interactions (Omeprazole and Iron salts). According to the list of Beers, 5.8% of seniors take drugs that classified as having some indications (hydroxyzine, amitriptyline).
Conclusions: Regarding polypharmacy, 42% of elderly are polymedicated with an average of about 5 different drugs per day, antihypertensives and antacids the most prescribed. Hypertension and depression are highly associated with polypharmacy. We identified