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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

ABSTRACTS

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Abstract Code: P-001

Effects of Methylphenidate Treatment for Attention-Deficit/Hyperactivity Disorder on Trauma Related Accident and Emergency Admissions: Self-Controlled Case Series Study

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Background: Patients with attention-deficit/hyperactivity disorder (ADHD) are prone to sustaining trauma that requires emergency room (ER) admission [1]. Evidence that pharmacotherapy for ADHD lowers the ER admission rates is limited.

Objective: To investigate the association between methylphenidate and trauma related emergency room (ER) admissions.

Method: 17,381 patients aged 6–19 years who received at least one methylphenidate (MPH) prescription were identified using the Hong Kong Population-based electronic medical records on the Clinical Data Analysis & Reporting System (2001–2013). Using a self-control case series [2] study design, relative incidence of trauma related ER admissions comparing periods when patients were exposed to MPH with non-exposed periods.

Results: Among 17,381 patients prescribed MPH, 4,934 had at least one trauma related ER admission. The rate of trauma related ER admission was lower during exposed compared to non-exposed periods (IRR = 0.91, 95 % CI 0.86–0.97). The findings were similar when only the first trauma episode was assessed (IRR = 0.89, 95 %CI 0.82–0.96). Similar protective association was found in both male and female patients. In validation analysis using non-trauma related ER admissions as a negative control outcome, no statistically significant association was found (IRR = 0.99, 95 % CI 0.95–1.02). Sensitivity analysis testing for uncertainty over the precise period of MPH exposure demonstrated consistent results.

Conclusion: This study supports the hypothesis that MPH reduces the risk of trauma related ER admission in children and adolescents. Long term MPH treatment is shown to prevent injuries in this group of high-risk patients and this potential benefit should be considered in clinical practice.

Table 1

	IRR	LCL	UCL
Trauma related ER admission (n = 4,934)			
All episodes	0.91	0.86	0.97
Gender			
Male (n = 4,309)	0.92	0.86	0.98
Female (n = 625)	0.83	0.68	1.00
First episode only	0.89	0.82	0.96
Gender			
Male (n = 4,309)	0.90	0.83	0.99
Female (n = 625)	0.73	0.57	0.94

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Abstract Code: P-002

Retrospective Evaluation of Polymorphisms of Angiogenesis in Patients Treated with Sorafenib

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Background: In the case of advanced hepatocellular carcinoma the only treatment able to increase the survival of patients (from 7.9 to 10.7 months) is the treatment with sorafenib [1], a multi-tyrosine kinase inhibitor, approved in 2006 by the Food and Drug Administration (FDA) as first-line treatment. This drug inhibits the proliferation of cancer cells and tumor angiogenesis in a broad spectrum of tumors.

Aim: This study was conducted with the aim of verifying whether the progression free survival (PFS) and overall survival (OS) are influenced by a particular pattern of polymorphisms. PFS was calculated from the date of treatment's initiation with sorafenib to the date of instrumental or clinical disease progression. Overall survival is defined as the time interval between start of treatment and death or last follow-up visit.

Methods: In this study the genetic polymorphisms of endothelial nitric oxide synthase-variable number tandem repeats (eNOS VNTR) has been analyzed. A retrospective no profit study has been conducted in patients with a diagnosis of advanced hepatocellular carcinoma. The analysis included: (a) extraction of genomic DNA from peripheral blood; (b) assessment of the concentration of the extracted DNA; (c) amplification of the regions of interest by PCR; (d) verification of the amplification on agarose gel; (e) purification of the amplified PCR; (f) reaction sequence; (g) purification of the products of the sequence, denatured and loaded on the sequencer; (h) analysis of the results.

Results: For No.14 of the analyzed patients the analysis of the polymorphism eNOS VNTR was conducted. For No.8 patients an allelic distribution 4a/b has been reported, while for No.6 patients an allele distribution 4b/b has been reported. The two polymorphisms differ in terms of PFS: median PFS (months) was 7.8 for 4b/b and 6.4 for 4a/b.

Conclusion: This result, if confirmed in a larger series of patients, lead to the execution of a phase 3 study that will assess whether the polymorphism 4a/b is responsible for a greater effectiveness of drug therapy with sorafenib. This study examined how the possible association between polymorphisms in the eNOS gene may influence the progression-free survival (PFS) and overall survival (OS). The present study, if the data will be confirmed by a larger sample of patients, will highlight how the presence of the eNOS gene 4a/b VNTR may be indicative of a positive response to sorafenib.

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Abstract Code: P-003

Risk and Benefit Evaluation of Oral Ketoconazole: A Review from Taiwan Adverse Drug Reaction Reporting System and Health Insurance Database

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Introduction: Oral ketoconazole is indicated for treatment of fungal infections and has also been used in advanced prostate cancer and Cushing's syndrome. In July 2013, EMA suspended this product because the risk of liver injury is greater than the benefit in treating fungal infection [1]. Concurrently, FDA decided to restrict its indication and added several warnings to manage the risk [2].
Aim: To evaluate the risks associated with oral ketoconazole use and to explore the usage patterns of oral ketoconazole in real clinical practice in Taiwan.
Methods: By using Taiwan National ADR Reporting System database, we reviewed all ADR reports related to oral ketoconazole from July 2007 to September 2013. Prescription pattern of oral ketoconazole was evaluated by using a longitudinal cohort dataset with one million individuals sampled from the National Health Insurance beneficiaries (LHID).
Results: We identified 58 ADR reports associated with oral ketoconazole in the database, including 40 (69 %) females and 18 (31 %) males. Among these reports, oral ketoconazole was indicated mainly for minor skin fungal infection or tinea. Hepatobiliary disorders (53 %) were most reported, including fatalities and liver transplantations. By using LHID, we identified 24,704 oral ketoconazole prescriptions in 2011, which was 10 times greater than any other antifungal agents. 77 % of the prescriptions were prescribed in physician clinics, where regular liver profile monitoring is less likely to put into practice in our society. Besides, since ketoconazole related liver injury may occur early even when commenced with recommended doses, it is not feasible to come up with a risk management plan to adequately reduce the risk. We also observed six Cushing's syndrome patients and 110 prostate cancer patients treated with oral ketoconazole in LHID.
Conclusions: In consideration of current clinical practice in Taiwan, along with the seriousness of the hepatic risk associated with oral ketoconazole use and the substitutability of oral ketoconazole in treating fungal infections, we believe the benefits of oral ketoconazole use did not outweigh the risks. Therefore, a recommendation of suspending the marketing authorizations of oral ketoconazole is preferred. For Cushing's syndrome and prostate cancer patients, authorities should ensure oral ketoconazole availability in controlled conditions.

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Abstract Code: P-004

Self Medication and Self Prescription. Relevance in Daily Medicine

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Introduction: Self medication of over the counter (OTC) medication or self prescribing of non OTC medication can cause great problems of patients' security when this attitude is used without responsibility. Self prescribing of non OTC also demonstrates a defect in pharmaceutical systems because patients can access to drugs without a prescription.
Aim: The aim of this study was to determine different patterns of self medication and self prescription and complications caused by these situations in general population, ambulatory patients and hospitalized patients.
Material and Methods: The study was performed in the pharmacovigilance committee of a tertiary care hospital in Buenos Aires, Argentina. We performed a questionnaire to determine self medication and self prescription patterns in three different groups: ambulatory care patients, hospitalized patients and general population. The questionnaire also asked about complications of this medications and groups of drugs involved in these situations.
Results: 448 questionnaires were performed; 203 in hospitalized patients, 149 in ambulatory care and 96 in general population. The global percentage of self medication and self prescribing both together was 75.44 % (CI 95 % 71.46–79.43 %); in ambulatory care 55.03 % (CI 95 % 47.04–63.02 %); hospitalized patients 85.22 % (CI 95 % 80.33–90.10 %) and general population 86.45 % (CI 95 % 79.61–93.30 %). Adverse drug reactions appeared globally in 9.37 % (CI 95 % 6.67–12.07 %); in ambulatory care 11.40 % (CI 95 % 6.30–16.51 %); hospitalized patients 8.86 % (CI 95 % 4.95–12.77 %) and general population 7.29 % (CI 95 % 2.09–12.49 %). Only 18 ADRs were serious, none fatal. Considering only self prescribing, the incidence was globally 19.86 % (CI 95 % 16.17–23.56 %), with a greater incidence in the group of general population. The groups of drugs involved most frequently in self medication and self prescribing were NAIDs, acetylsalicilic acid, anticholinergic and amoxicillin.
Conclusion: Although self medication is a common practice, it seems to be a secure practice. Self prescription practice is unacceptably high because indicate that patients could access to medication without a prescription, including benzodiazepines. The group of ambulatory care has the lowest incidence of self medication, perhaps because they consult a physician instead of using medication directly.

Abstract Code: P-005

Economic Burden of ADRs in a Tertiary Care Hospital

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Introduction: The economic burden of adverse drug reactions is increasing in almost every health system, not only direct costs but also indirect ones. Some reasons of this increasing problem are the increasing incidence of ADRs and the greater complexity of patients receiving polimedication.
Aim: the aim of this study was to determine the economic burden of adverse drug reactions in a tertiary care hospital, both direct and indirect costs.
Material and Methods: The study was performed in the pharmacovigilance committee of a tertiary care hospital (Hospital General de Agudos Dr Cosme Argerich) in Buenos Aires, Argentina, with approximately 350 beds. The information of ADRs was from July 2008 to June 2013. Costs of diagnosis, treatment and rehabilitation of ADRs were included in direct costs and absence from work and school were considered as indirect costs.
Results: In this period there were 2,830 ADRs. The total indirect costs in this period were 266,737.72 American dollars; the total direct costs were 287,558.86 American dollars. The indirect costs that could be prevented were 80.393,61 American dollars and the direct costs that could be prevented were 87,809.06 American dollars. The services with higher costs in ADRs were internal medicine, nephrology and unit of intensive care. During all this period, and evaluated in semesters, the costs were similar showing no improvement in prevention of ADRs.
Conclusion: Direct and indirect costs of ADRs were very high and approximately one third of them were preventable. There was no improvement in diminishing preventable costs along time. We need more education in health professionals to reduce costs. Costs are similar to other in developing countries and lesser than developed countries.

Abstract Code: P-006

Selective Serotonin Reuptake Inhibitor Exposure during Pregnancy and Risk of Autism Spectrum Disorders in Children: A Meta-Analysis of Observational Studies

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Introduction: Selective serotonin reuptake inhibitor (SSRI) use during pregnancy has been associated with preterm birth, low birth rate, congenital malformation and persistent pulmonary hypertension [1–3]. Yet, the effects of perinatal SSRI exposure on autism spectrum disorder (ASD) in children remain controversial, and corresponding meta-analysis is currently lacking.
Aim: To investigate the association between SSRI exposure during pregnancy and risk of ASD in children.
Method: Electronic databases were searched for observational studies related to the association between SSRI exposure during pregnancy and ASD in children from January 1946 to May 2014. Studies with cohort and case–control designs were included. Data relevant to the measure of association between the SSRI exposure during pregnancy and ASD in children were extracted and compiled for meta-analysis evaluation. Pooled estimates were obtained by the generic inverse variance method and the random-effects model was used to address heterogeneity between studies.
Results: Eighty citations were identified. Seven observational studies were identified and six studies were included. Four case–control studies were eligible for meta-analysis and two cohort studies were narratively reviewed. The pooled crude and adjusted odds ratios of the case–control studies were 2.13 (95 % CI 1.66–2.73) and 1.81 (95 % CI 1.47–2.24) respectively. No heterogeneity was observed between studies ($I^2 = 0$ %). The two population-based cohort studies, which utilized the same Denmark data set, have conflicting results [4–5]. Sorensen et al 2013, reported significant results [adjusted HR 1.6 (95 % CI 1.3–2.0)] [4], while Hviid et al demonstrated non-significant results [fully adjusted RR 1.20 (95 % CI 0.90–1.61)] [5]. In Hviid et al.'s study however, further subset analysis showed statistically significant results in SSRI use from 2 years to 6 months before pregnancy [adjusted RR 1.46 (95 % CI 1.17–1.81)].
Conclusions: The findings of this meta-analysis and narrative review support the association between SSRI exposure during pregnancy and ASD in children. However the result is limited by the variability in the quality of studies as indicated by the Newcastle-Ottawa scale scores between 7 and 9.
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Abstract Code: P-007

Unifying Drug Safety and Clinical Databases

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Clinical and drugs safety organisations run their operations independently and use separate databases designed to comply with different data standards. This separation is neither efficient nor effective since investigators need to report serious adverse events both to the clinical and drug safety departments, causing the respective databases to contain partially overlapping data sets

containing common elements that need to be reconciled. Electronic data capture provides the opportunity to avoid duplicate storage and obviate reconciliation. It also introduces the risk of non-compliance due to late submission of unexpected serious adverse reactions to competent authorities. This raises the potential for a clinical department to receive a case that the drug safety department is unaware of. However, the most significant inefficiency probably lies in the preparation of aggregate reports and regulatory documents that need to be prepared using data originating from both databases. For example, signal detection and evaluation needs to utilize data originating from both the clinical and safety database, but the safety database typically does not contain non-serious adverse reactions originating from clinical trials or laboratory data. This information is included in the clinical database to which drug safety does not always have immediate access.

Maintaining two databases with partially overlapping information increases costs and risks causing unnecessarily challenging information flow and not clear responsibilities. In a resource-constrained world these issues are particularly relevant since unnecessary activities and associated costs drain resources from scientific assessment of drug safety data and risk minimization activities thereby hampering patient safety [1].

Luckily, unifying the drug safety and clinical database is not utopia. The Clinical Data Interchange Consortium (CDISC) has set the standards for clinical trial data, while the International Conference of Harmonization (ICH) dictates drug safety ones. CDISC is expanding its Clinical Data Acquisition Standards Harmonisation (CDASH) model to capture adverse event data associated withICHE2B. All common data items have two labels that have been mapped. This exercise is showing that there is no scientific justification for segregation. The differences between these two standards can be attributed to conventions or arise from new technology that renders unnecessary the keying in of certain context information (dates, times and recorder ID). Once this mapping is completed then a common data acquisition process will become feasible. This is the prerequisite to ultimately unifying the two databases and to implementing more efficient processes.

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Abstract Code: P-008

Congenital Malformations of Fenugreek in Morocco: An analysis of Reports in the Moroccan Herbal Products Database from 2004 to 2014

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Introduction: In Morocco, Trigonella foenum graecum (fenugreek) is used mainly as a tonic, as a remedy against diabetes, as a galactogogue and for stimulation of appetite [1]. It is recommended during pregnancy because natural and to avoid conventional chemical drugs.

Aim: To describe the Moroccan experience in terms of fenugreek associated with congenital malformations.

Methods: The Moroccan pharmacovigilance of herbal products (HP) database was analyzed in a retrospective manner from January 1, 2004 to April 30, 2014. The database contains patient demographics, adverse effects associated with HP, and details on seriousness, causality and outcome. Descriptive statistics were used for data analyses.

Results: 196 cases (7.3 %) of adverse effects to fenugreek were reported. Among these cases, 101 cases (51.3 %) were associated with congenital malformations. Patients were aged 20–46 years (mean 28.9 $\pm$ 5.9 years). Fenugreek seeds were obtained from herbalists and were used for a number of folk medicine indications: stimulate appetite (3 cases), bronchitis (1 case), fever and abdominal pain (1 case), inflammation (1 case), cough (1 case), asthma (1 case), galactogogue (3 cases) and mainly as a fortifying food (90 cases). All reported cases were from oral ingestion. The pregnancy trimester when fenugreek seeds were taken was: 1st trimester (34.6 %), 1st and 2nd trimester (3 %), 1st, 2nd and 3rd trimester (60.4 %), unknown (2 %). Congenital malformations concerned were encephalocele, hydrocephalus congenital, spina bifida, cleft palate, anencephaly, malformations multiple, hypospadias, dwarfism, clubfoot, genital malformation, brain malformation, nose malformation congenital, dextrocardia, finger malformation and death foetal. A potential signal has been detected in relation with fenugreek and has concerned twelve foetal disorders. The WHO causality assessment was assessed to be "possible" in all cases.

Discussion: Many factors could explain the congenital malformations reported mainly maternal folic acid deficiency, embryopathy, maternal diabetes [2], genetic, environmental and nutritional factors, drug consumption such as cyclophosphamide [3], and fenugreek phytoestrogens. The majority of malformations are multifactorial in origin. But it is important to note that for all these women in our database, many important data are missing (history: infertility and diabetes; drugs taken; dose of fenugreek used; etc.).

Conclusions: Fenugreek has been suggested for many uses, based on tradition. These uses have not been thoroughly studied in humans, and there is limited scientific evidence about safety or effectiveness. Further epidemiological studies among pregnant women and experimental investigations of the foetal disorders should be conducted and this is clearly an important area of future research.

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Abstract Code: P-009

New Signal Management: Lower Limb Edema Induced by ERIP-K4

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Introduction: In October 2012, the Global Fund has supported Moroccan Pharmacovigilance in the National TB Program for management the adverse effects of anti-TB drugs. The objective of this work was to research and manage signals of TB Pharmacovigilance.

Methods [1, 2]:

- Source of data: individual cases safety reports (ICSRs) from TB health care professional of Moroccan Tuberculosis Control Program (MTCP).
- Frequency of data: 24 ADRs of lower limb edema between October 2012 and December 2013 with combinated form of anti-TB drug.
- Signal detection methods: qualitative method: case by case review of ICSRs from MTCP. Quantitative method: ratios of disproportionality: proportional reporting ratio (PRR), reporting odds ratio (ROR) from national database and information component (IC) from international database.
- Signal assessment: quality of evidence for causality.
- Decision making following assessment
- Stakeholder communication

Results: Twenty four lower limb edema have been reported from 8 different regions of Morocco. Patients had no particular history, with an average age of 39.3 ± 17.3 years, a sex ratio of 1.5. The time to onset of these edemas varied from 1 to 90 days. Hepatic and renal function tests of these patients were normal. Quantitatively, the PRR was 7.5, the ROR was 7.9 and the IC was 2.03. Qualitatively, this effect is not described in the literature. Accountability of these effects was possible without signal impact. The decision of the Technical Committee of Pharmacovigilance was to continue monitoring, to start an active surveillance and to communicate the signal to stakeholders.

Conclusion: Lower limb edema are a new signal of antituberculosis drugs discovered through the integration of Pharmacovigilance in the Moroccan Tuberculosis Control Program.

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Abstract Code: P-010

Palonosetron: Similarities and Differences in the Safety Profile as Compared to Other Drugs of the Same Class

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Background: Palonosetron is a 5-HT_3 receptor antagonist with a safety profile similar to that of other drugs of the same class, but with unique features. QT interval prolongation is a class effect, however, the extent and clinical significance of this adverse effect diverges between the 5-HT_3 antagonists.

Results: An integrated analysis of 1819 cancer patients, enrolled in 3 studies, showed that the effect on the QTc parameter by Fridericia correction (QTcF) was 2 ms for both 0.25 and 0.75 mg of intravenously administered palonosetron as compared to baseline, while it was 5 ms for both 32 mg ondansetron and 100 mg dolasetron [1]. Furthermore, 230 healthy volunteers were enrolled in a thorough QT/QTc study to evaluate the effect of 0.25, 0.75 and 2.25 mg of intravenous palonosetron (ninefold the most commonly administered dose) versus placebo and 400 mg moxifloxacin (positive control). The time-matched analysis of the upper side 95 % ANOVA model based confidence limit compared to placebo and baseline corrected showed that QT prolongation was less than 10 ms at all the tested palonosetron doses, while it was more than 10 ms for moxifloxacin [2]. In a healthy adults study, the maximum mean (95 % upper confidence bound) difference in QTcF from placebo after baseline-correction was 19.5 (21.8) ms for 32 mg of ondansetron and was predicted to be 9.1 (11.2) ms for the 16 mg dose [3]. In a similar study evaluating dolasetron doses of 100 mg and 300 mg, the maximum mean (95 % upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 14.1 (16.1) and 36.6 (38.6) ms for the 100 mg and 300 mg dolasetron doses, respectively [4]. The aforementioned results prompted the contraindication of dolasetron use in chemotherapy induced nausea and vomiting, while for the same indication the maximum dose of ondansetron was reduced by half. Cumulatively, our safety database yields 3 reports of QT interval prolongation, considered to at least be possibly related to palonosetron. All of them show the concomitant presence of confounding factors such as chemotherapy or anaesthetics.

Conclusions: Overall, the data originating from all 3 studies and spontaneous reporting show that the effects of palonosetron on QT interval are negligible and no clinically relevant changes have been documented.

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Abstract Code: P-011

Palonosetron: 10 Years of Post-Marketing Use

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Background: Palonosetron hydrochloride (Aloxi®, Onicit®, Paloxi®) is a potent and highly selective serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor and long elimination half-life. The drug is indicated for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic chemotherapy (MEC/HEC), as well as post-operative nausea and vomiting (PONV). A 0.25 mg intravenous formulation of palonosetron was approved in the USA in July 2003 and in the EEA in March 2005 for the prevention of CINV. In addition, an oral formulation (500 mcg softgel capsule) was approved in the USA in August 2008 and in the EEA in May 2010, while a 0.075 mg intravenous formulation was

approved in the USA in March 2008 for the prevention of PONV. Palonosetron is currently approved for adult use only in over 70 Countries worldwide, including Japan.

Methods: A post-marketing surveillance (PMS) review was conducted to evaluate palonosetron's safety profile from September 2003 (launch date in the USA) to February 28, 2014. All spontaneous Individual Case Safety Reports (ICSRs) collected and processed in the Helsinn Global Safety Database (ARGUS® by Oracle, USA) were comprehensively analyzed.

Results: Overall, palonosetron has shown a satisfactory safety profile. PMS data comprises 437 spontaneous ICSRs (with 1033 events) collected globally; 136 (with 402 events) were considered serious and 301 (with 631 events) non-serious. In the same period, approximately 7.068 million patients worldwide were treated with palonosetron (all formulations). The number of ICSRs generated by the worldwide spontaneous reporting system is reflected in a crude reporting rate of approximately 0.019 palonosetron serious ICSRs (all SOCs) per 10^3 patients exposed. The most important adverse reactions such as hypersensitivity, QT/QTc prolongation, convulsive events, and constipation are shared with other drugs of the same class. In the case of QT/QTc prolongation, no reported cases were associated with life threatening arrhythmias such as torsade de pointes. Even by taking into account a usually accepted degree of under-reporting, this crude figure is low and supports the overall good safety profile of palonosetron.

Conclusions: After a more than 10-year presence on the worldwide market and more than 7 million patients treated, the established benefit-to-risk profile of palonosetron is confirmed to be favourable.

Abstract Code: P-012

Performance Comparison between Time-to-Onset and Disproportionality-Based Signal Detection Methods on Simulated Data

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Background: Adverse events (AEs) occurring after vaccination are monitored for safety reasons. Some are vaccine-related whereas others are unrelated (coincidentally occurring after vaccination). Some statistical methods to detect vaccine-related AEs are based on measures of disproportionality between a vaccine and an AE. These disproportionality measures disregard the time-to-onset (TTO) distribution of AEs after vaccination. However, it has been shown that TTO distributions, when analysed by Kolmogorov–Smirnov tests, can be very useful for signal detection [1, 2]. The characteristics of the TTO distribution for vaccine-related AEs are expected to affect the performance of the Kolmogorov–Smirnov test.

Objective: To evaluate the performance of 3 statistical tests in TTO signal detection, using simulated data for different TTO distributions of vaccine-related AEs in a background of unrelated AEs. Performance of the relative risk (RR), a disproportionality method, was used as a benchmark.

Methods: Gamma distributions with various means and variances (G_{MV}) were randomly generated to simulate the TTO of vaccine-related AEs, while uniform distributions simulated unrelated ones. We assumed a typical AE with a background incidence of 20/10,000 within an observation period of 100 days, generating 20 cases uniformly distributed. For each G_{MV}, a number (x: between 1 and 50) of gamma-distributed vaccine-related AEs were added to the uniform distribution. For each G_{MV} and for each total number of AEs (20 + x), 3 statistical tests (Kolmogorov–Smirnov, Cramer–von Mises and Anderson–Darling) were performed to test the null assumption of uniform distribution. For each x, performance was measured as the percentage of significant tests ($\alpha = 0.05$) over 100 simulations. To calculate the RR, we assumed a control group of the same size with 20 unrelated AEs.

Results: The RR was significant with 15 or more vaccine-related AEs. By contrast, for the 3 TTO statistical tests, there was a high percentage of significant tests (> 80 %) with 8 or more vaccine-related AEs, with gamma distributions characterised by low means. The Anderson–Darling test was the best performer, especially for distributions representing AEs that occurred shortly after vaccination.

Conclusions: In some cases, depending on the temporal relationship between the vaccine and the related AE, TTO signal detection performs better than disproportionality measures. As signal detection is supposed to be exploratory and because temporal relationships are a priori unknown we recommend the routine use of TTO methods for signal detection, simultaneously with measures of disproportionality, when the presence of an appropriate control group makes it possible.

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Abstract Code: P-013:

Risk Management of Anti-TB Drugs Induced Liver Injury in Morocco

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Introduction: Hepatic adverse drug reactions (ADRs) pose a problem of patient adherence to treatment and can be life-threatening for TB patients. No guideline for managing hepatic ADRs has been validated globally [1–3] .The objective of this work was to prevent and manage the risk of anti-TB drugs induced-hepatic ADRs.

Methods: In October 2012, the Global Fund has supported Moroccan Tuberculosis Control Program (MTCP) for management ADRs of anti-TB drugs. Several individual cases safety reports (ICSRs) from TB health care professional have been collected after sensitization sessions in pharmacovigilance. To assess the risk, we calculated 2 ratios of disproportionality: proportional reporting ratio (PRR) and reporting odds ratio (ROR) in the national database. The Moroccan Pharmacovigilance Center (MPVC) with collaborating some hepatologist and phthisiologists developed a practical procedure of TB hepatotoxicity that helps prescribers to manage the risks associated with anti-TB drugs.

Results: 432 ADRs of anti-TB drugs were collected between October 2012 and December 2013 including 80 (18.5 %) of hepatic disorders, preceded by digestive (21 %) and cutaneous (24.2 %) disorders. The

average age of patients who had hepatic ADRs was 43.5 ± 19.1 years, with a sex ratio of 0.7. The average time to onset of hepatic ADRs was 28.0 ± 24.8 days. Hepatic cytolysis was the most predominant effect (61.4 %). Our study recorded 6 deaths, including 4 due to liver injury. The PRR was 9 and ROR was 8.4. The Moroccan Technical Committee of Pharmacovigilance decided to performing a prevention and management procedure of hepatic ADRs, adapted to our Moroccan context to TB stakeholders, which aims to minimize the risks associated with these effects (Logigram).

Conclusion: The management of anti-TB drugs induced liver injury adapted to the context of each population, is the only way to minimize the TB morbidity and mortality.

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Abstract Code: P-014

Current Reporting Status & Challenges of Asian Countries—National Centres for Pharmacovigilance under WHO-UMC

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Introduction: Asia is one of the populous continents in the world with approximately 4.3 billion populations. Asia's pharmaceutical market currently is worth more than $140 billion and is the third largest pharmaceutical market in the world, after North America and Europe. Japan and China are the two largest drug markets, accounting for about 70 % of the total value, followed by India, Korea, Hong Kong, Singapore, Malaysia, Indonesia, Thailand, Philippines, and Vietnam. Foreign drug manufacturers are also strengthening their presence in Asia, particularly in India and China. Over the next few years, it is predicted that China will become the second largest pharmaceuticals market in the world, with the sales estimated to reach $160 billion, followed by India. This increased demand has brought an intensified focus on pharmacovigilance (PV) and drug safety in this region. A total of 27 countries from Asia participated under WHO-UMC for international drug safety monitoring till 2013. So far, 975828 (10.96 %) Individual Case Safety Reports (ICSRs) have been committed to WHO-UMC: International drug safety database system "VigiBase" (International ICSR database system developed & hosted by UMC) from Asian national Pharmacovigilance centres.

Method: We performed a retrospective observational study of the ICSRs reported to the WHO-UMC's ICSRs database i.e. ViziLyze from 1972 to 6th May 2014. All drugs were classified using the anatomical therapeutic chemical (ATC) classification code system, and all the reactions were classified using the WHO-ART code system and subsequently entered into this database.

Results: Out of 975,828 ICSRs 527,669 (54 %) were from females & 416,883 (43 %) ICSRs were from males followed by 31,276 (3 %) ICSRs with unknown gender. For reported ICSRs, 373,211 (38 %) consist of skin and appendage disorders, 187,000 (19 %) consist of Gastro-intestinal system disorders, 165,638 (17 %) consist of Body as whole-general disorders followed by 114,269 (12 %) consist of Central & peripheral nervous system disorders. Among 27 countries from Asia, the top five contributors to VigiBase are as follow: 343,474 (35 %) Korea, 216,472 (22 %) Thailand, 109,555 (11 %) Japan, 98,072 (10 %) Singapore and 73,700 (8 %) India.

Conclusion: In terms of population, Asia hosts nearly 60 % of world current population & current contribution of Asian-National Pharmacovigilance Centre's to WHO-UMC's VigiBase is 10.96 %, but till date there is no coordination & harmonization among 27 Asian National Pharmacovigilance centres & regulatory authorities in comparison to continents like USA & Europe under WHO-UMC for the identification of drug safety signals.

Abstract Code: P-015

Spontaneous Reporting of Adverse Events Due to Herbal Products in Pharmacovigilance Programme of India

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Introduction: Herbal products (HP) are widely used as pharmaceutical and neutraceutical agents in India. Pharmacovigilance Programme of India (PvPI) is an essential tool for developing reliable information on the safety of herbal medicines as used in India. The existing system allows reporting adverse events related allopathic and herbal medicine and encourages monitoring the safety of them.

Objective: To analyse the suspected adverse reactions reported with the use of HM in India

Method: All reports of suspected adverse reactions to HPs reported to National Coordination Centre (NCC)forPvPI during the period 2011 July–December 2013 were assessed on causal link between use of the medication and the reported adverse reaction. Adverse reactions were classified by severity according to international standards. An overview was made of all reports of severe adverse reactions.

Results: The NCC-PvPI database contained 39 reports of suspected adverse reactions to HPs in which sixteen of them were classified as serious, twelve were non serious and eleven were unknown. The cases were categorized by system organ classification and it was found that 52.5 % were skin and appendages disorders. The suspected herbal medicines and HPs were Gudmarameda, Shankhpushpi, Mahavatvidhwansan, Dashmoolkwath, shemaryesaka, Melas cream, senna extract, aloe, mustard oil, digitalis, garlic, menthol and turmeric. Causality assessment as per WHO scale reveals that five cases were probable/likely, seventeen were possible, one was unlikely and rest of them were unassessable or blank.

Conclusion: The adverse events related to the use of herbal products reported under PvPI, are attributable either to poor product quality or to improper use. Since the current PvPI suffers from scarcity of safety data on HP, healthcare providers must be educated to report and to ensure the safe use of HPs.

Abstract Code: P-016

Dermatological ADRs in Indian Population-Three-Year Report of Pharmacovigilance Programme of India

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Introduction: India is one of the member country under WHO-UMC for international drug safety monitoring since 1998. But Indian Pharmacopoeia Commission is an Autonomous Institution under Ministry of Health & Family Welfare, Government of India & functioning as National Coordination Centre for Pharmacovigilance since 15th April 2011. For the year 2013, India stood at 7th position among 118 member countries under WHO-UMC for ADR reporting & have contributed 2 % to the global data. In addition to this, India leading at 3rd position among 27 member countries in Asia under WHO-UMC.
Objective: Our objective was to assess the spontaneous reports of adverse drug reactions causing Dermatological ADRs in Indian population from May 2011 to April 2014.
Methods: The spontaneous reports of 18123 patients were retrieved at national pharmacovigilance centre from the database containing all Skin & Appendages ADR reports from 90 ADR Monitoring Centres (AMCs) in India under Pharmacovigilance Programme of India (PvPI) from May 2011 to April 2014. These reports were analysed for various characteristics of patients, drugs and Skin & Appendages ADRs using a search and analysis tool.
Results: Of the 18123 individual case safety reports (ICSRs), more ICSRs were reported from the female (50 %) than the male patients (49 %). The 18 % patients were found to be serious, 66 % patients were non-serious & 16 % unknown for the reported ICSRs caused Skin & Appendages disorders. The top five ADRs causing Skin & Appendages disorders as follow: rashes (43 %), other skin reactions (23 %), hypotrichosis (16 %), Urticaria (6 %) & erythema multiforme (5 %).
Conclusion: Of all the ADRs under Skin & Appendages, the incidence of Stevens Johnson syndrome is increasing year by year in Indian population & is 7th leading ADR under Skin & Appendages for the reported ICSRs in Indian patients drug safety database i.e. VigiFlow.

Abstract Code: P-017

A Survey on Pharmacovigilance Awareness Amongst Physicians in Major Cities of Pakistan

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Introduction: WHO defines Pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any possible drug-related problems" [1]. Globally, adverse drug reactions (ADRs) are a major cause of morbidity and mortality [1] and rank among the top 10 leading causes of mortality in many countries [2]. Approximately, 6.5 % of hospital admissions are because of adverse drug reactions that can add exorbitant cost to healthcare expenses in fund strapped developing economies [3]. It is vital to evaluate and monitor safety of medicines in clinical use to prevent and reduce harm to patients thereby contributing to public health [4].
Aim: To assess the awareness of Pharmacovigilance amongst physicians practicing in various institutions, hospitals and clinics in major cities of Pakistan.
Methods: A cross-sectional survey was conducted during Getz Pharma sponsored academic exercise in Karachi, Islamabad and Lahore from December 2013–April 2014. The participants were gastroenterologists, diabetologists, cardiologists, internists, surgeons, and others. A questionnaire was designed and surveyed amongst 242 doctors, the data was analyzed using SPSS v.20.
Results: From 242 participating doctors, 212 (87.6 %) responded to all the survey questions. Out of these, 211 (99.53 %) appreciated Getz Pharma's initiative of Pharmacovigilance awareness program. Amongst the responders, 196 (92.45 %) were clear on the basic concept of Pharmacovigilance, 209 (98.58 %) were of the opinion that Pharmacovigilance program of Getz Pharma is beneficial in improving the health of our community and 196 (92.45 %) participants were interested to learn more about Pharmacovigilance.
Conclusion: The results of the above survey suggest that majority of physicians have basic concept of Pharmacovigilance and consider such initiatives as beneficial to community's health. This survey can further be extended to other cities and regions in Pakistan to better understand the awareness of Physicians on Pharmacovigilance.
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Abstract Code: P-018

Evaluation of Adverse Drug Reactions Among In-Patients Admitted into the Adult Medical Wards of University of Ilorin Teaching Hospital, Nigeria

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Introduction: Adverse drug reactions (ADRs) are considered as one of the prominent causes of death among hospitalized patients [1 − 2]. With increased access to newly introduced essential medicines, there is a greater need to monitor and promote their safety and effectiveness. Although many drugs have been used and studied in developed countries, their safety profiles may not necessarily be applicable to other settings, where

the incidence, pattern, and severity of adverse drug reactions (ADRs) may differ because of local environmental and genetic influences [3].

Aim: To detect, analyze and quantify the type and frequency of ADR and identifiable factors associated with adverse drug reactions in the adult medical wards of University of Ilorin Teaching Hospital, Nigeria.

Methods: A prospective spontaneous reporting study was conducted over a period of one year on all admissions in the medical wards. Data were extracted from daily adverse drug reactions reports from March 2013 to February 2014. The extracted data were analyzed descriptively using SPSS version 20.

Result: A total admission of 2012 patients, consisting of 910 males and 1102 females were assessed for ADRs in the wards and reported, fifty-two (2.58 %) ADR was detected and reported. 30 (57.7 %) of total reported ADRs cases were patients admitted specifically due to ADR. Twenty-one (40.4 %) of ADR reported occurred while on admission. Drug classes most implicated were analgesics (21.2 %), hypoglycemic agents (15.4 %), hypotensive agents (11.5 %), and antipsychotic (9.6 %). Commonly affected organ/systems were CNS (36.4 %), GIT (20 %) and CVS (16.4 %). For an outcome of ADR, thirty-nine (75 %) patients had full recovery, nine (17.3 %) patients had a prolonged hospital stay, and two (3.8 %) patients recovered fully but with disability. Admission specifically due to ADR was evaluated to be 1.49 % of total admissions.

Conclusion: The study shows that ADR occurs among the inpatients in the adult medical wards. Reporting ADRs is of great importance in generating knowledge to enhance safety in drug use. There is need to educate the patients on responsible use of medicines. This may go a long way in reducing percentage of admissions due to ADRs.

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Abstract Code: P-019

Pharmacovigilance of Generic Medicines versus Originator Medicines

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Introduction: Monitoring the use and effect of medicines is an essential focus in order to achieve the goal of maintaining the highest safety standards. Generic medicines can only be marketed after the originator product has been available for many years, the effects of the active substances they contain are very well documented and their safety profiles are well established. In Morocco, according to the latest figures from IMS Health, in 2013, the generic medicines boxes sold increased by 4.1 versus 0.4 % for the originator medicines. Generic medicines represent 31.8 % of the private market' consumption. Whereas, generic medicines represented 90 % of the public market according to the Ministry of Health policy.

Aims: To compare the tolerance of generic medicines versus originator medicines and to identify the serious adverse effects attributable to both of them.

Methods: Retrospective analysis of the Moroccan Pharmacovigilance centre database from January 2013 to December 2013. Vaccines were excluded from the analysis. The data analysis was carried out from Vigibase. The analytical study relies on the comparison of the percentage of serious ADRs observed with generic medicines and originator counterparts. The Chi square test was used to compare the percentage, and the statistical significance level was set at $P < 0.05$.

Results: A total of 1130 individual case safety reports (ICSRs) met the inclusion criteria, which represented 73.8 % of the whole cases collected during this period. 51.7 % of these ADRs were related to generic medicines. The proportion of generics induced serious adverse effects was 11.2 versus 18.6 % related to originator medicines. Among the 27 deaths recorded during this period, 25 % were observed with generic medicines versus 75 % with originator medicines. The antimycobacterial drugs (52.6 %) and the antithrombotic agents (11.4 %) were the most involved therapeutic classes in the ADRs related to generic medicines versus Alimentary tract and metabolism therapeutic classes (72.7 %) for originator medicines.

Conclusion: This was the first Moroccan study focusing on the comparison between the tolerance of generic and originator medicines. The results highlighted the absence of evidence that generic medicines were more likely to cause serious ADRs. The results did not reflect the reality since the data analysis has been limited to the year 2013 .The Centre-Antipoison et de Pharmacovigilance du Morocco, is preparing to extend this study to all cases registered in this database in the future.

Abstract Code: P-020

Regulatory Action; Medical Inaction?

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Background: Regulatory agencies have warned repeatedly that oral diclofenac may be unsafe in patients with underlying heart disease [1 − 5]. The consensus is that diclofenac has an increased risk similar to that of COX-2 antagonists. Naproxen and low-dose ibuprofen are believed to be safer.

Aim: To assess whether these warnings have altered hospital prescribing of NSAIDs.

Method: We analysed the hospital prescribing data from 14 acute NHS Trusts in the West Midlands region of the United Kingdom. The data were accessed through the Define® software (Rx-info Ltd) which uses a standard dictionary to compare different hospitals' prescribing patterns. We compared the prescribing of the NSAIDs diclofenac, naproxen and ibuprofen to see if it changed over time.

Results: The ratio of diclofenac to ibuprofen plus naproxen is shown in the Table 1. We have shown our NHS Trust (hospital group) separately from all other Trusts in the region. Usage of diclofenac has fallen throughout the region but in other hospitals the decline has been at a slower rate.

Discussion: Our Trust (which hosts the ADR Centre) took action to reduce the usage of diclofenac following the publication of the Danish cohort study [6]. Usage in other hospitals has started to decline following repeated warnings from the MHRA and EMA. Regulators issue advice to Trusts but even in an age of easy electronic communication messages may take time to be turned into action. Price may play a part in decision-making as diclofenac is cheaper than naproxen but where a choice of drugs exists safety should be a major consideration in choosing between them. Regulators should be aware that it takes time to change prescribing habits after they take action.

Table 1 Ratio (diclofenac):(ibuprofen plus naproxen) oral usage by quarter in Sandwell and West Birmingham Hospitals NHS Trust and all others in the Region

Quarter	SWBH	Others	Regulatory action
2011Q3	1.42	1.27	Danish cohort study published
2011Q4	1.21	1.26	
2012Q1	0.43	1.19	
2012Q2	0.51	1.23	
2012Q3	0.22	1.17	
2012Q4	0.07	1.12	EMA press release, MHRA DSU article
2013Q1	0.07	1.03	
2013Q2	0.06	0.92	Further DSU article and MHRA press release
2013Q3	0.06	0.72	

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Abstract Code: P-021

Safety of Palonosetron and Ondansetron in Preventing Chemotherapy-induced Nausea and Vomiting in Pediatric Patients Receiving Moderately- or Highly-Emetogenic Chemotherapy

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Background: Palonosetron, a potent and selective 5-HT_3 receptor antagonist, is non-inferior to ondansetron in preventing chemotherapy-induced nausea and vomiting in pediatric patients.
Objective: Evaluate the safety of two dose-levels of palonosetron, versus ondansetron, in pediatric patients receiving moderately- or highly-emetogenic chemotherapy (MEC-HEC) in a multinational, randomized double-blind study.
Methods: Patients aged 64 days–16.9 years receiving palonosetron (low-dose: 10 mcg/kg, maximum dose 0.75 mg; high-dose: 20 mcg/kg, maximum dose 1.5 mg) and ondansetron (3 × 150 mcg/kg, maximum dose 32 mg) were assessed for safety [adverse events (AEs), laboratory and ECG evaluations].
Results: 494 patients received ≥ 1 dose of medication (167 low-dose, 163 high-dose palonosetron; 164 ondansetron). Treatment-emergent AEs (TEAEs) were numerically lower in the palonosetron groups (low-dose: 80.2 %; high-dose: 69.3 %) than in the ondansetron group (81.7 %). The most frequently reported were [system organ class (SOC)]: blood and lymphatic system (low-dose palonosetron; high-dose palonosetron; ondansetron: 53.3 %; 48.5 %; 59.1 %); gastrointestinal system (26.3 %; 25.8 %; 34.1 %); general disorders and administrative site conditions (24.0 %; 16.0 %; 19.5 %); infections and infestations (13.2 %; 12.3 %; 18.3 %). Drug-related TEAEs were more consistent across treatment groups (4.2 %; 4.3 %; 4.3 %), the most frequently reported being SOC nervous system disorders (1.8 %; 1.8 %; 1.2 %), mainly headache (1.8 %; 0.6 %; 1.2 %). Serious AEs (SAEs) were also numerically lower in the palonosetron groups (low-dose: 31.1 %; high-dose: 26.4 %) than in the ondansetron group (33.5 %). The most frequently reported SAEs were (SOC): blood and lymphatic system (21.0 %; 19.6 %; 24.4 %); gastrointestinal system (3.6 %; 1.8 %; 6.1 %); general disorders and administrative site conditions (6.0 %; 3.1 %; 4.3 %); infections and infestations (6.0 %; 2.5 %; 7.9 %). Three patients had treatment withdrawn due to febrile neutropenia (1 high-dose palonosetron; 1 ondansetron) and haemorrhagic stroke (1 high-dose palonosetron, resulting in death). All withdrawals and deaths (3 high-dose palonosetron; 4 ondansetron) were considered unrelated to the study drug. Laboratory and ECG evaluations, inclusive of the QT interval, raised no concerns.
Conclusion: Palonosetron does not present a significant risk to pediatric patients receiving MEC-HEC; results are consistent with the established safety profile. There were no fatal outcomes or discontinuations due to drug-related TEAEs. Both palonosetron doses are safe and well-tolerated. No clinically relevant differences between palonosetron and ondansetron were observed in the safety profile.

Abstract Code: P-022

Liver Injury in Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Review of 72 Cases

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Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a syndrome with multi-systemic involvements [1–4]. Liver injury is the most common visceral manifestation [2, 5, 6].
Aim: To investigate the types of liver injury and factors involved, including the chronology, recovery time, relationship with culprit drugs and the pathology among DRESS patients.
Methods: A retrospective medical record review was conducted in the DRESS patients treated at the National Taiwan University Hospital between December 2000 and January 2013. Inclusion criteria and liver injury were defined according to the International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR). The pattern of liver damage is classified according to the International Consensus Meeting Criteria.
Results: 72 cases were included in this study. Among them, 62 (86.1 %) had liver injury, with 6 (9.7 %) patients having liver injury before skin symptoms. We found 23 patients were cholestatic type (44.2 %), followed by 17 patients in mixed type (32.7 %) and 12 patients in hepatocelluar type (13.1 %). Patients in hepatocellular type were younger, with the median age of 31.5 ($P = 0.044$). They had higher frequency (88.3 %) of having liver function tests above 10 times of upper normal limits (the extreme group), comparing to the cholestatic and mixed types (39.1 and 58.8 %, $P = 0.042$). Patients in extreme group were younger, with median age of 33 ($P = 0.012$). When comparing with non-extreme group, the extreme group tended to have fever (90.9 versus 65.5 % in non-extreme group, $P = 0.026$) and had less eosinophil on skin biopsy (30.8 versus 88.9 % in non-extreme group, $P = 0.002$).
Conclusions: Liver injury might be a prodrome of DRESS. DRESS patients with hepatocellular type liver injury are younger, with higher liver function tests, slow recovery, and less eosinophil on skin biopsy.
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Abstract Code: P-023

Adverse Reaction Monitoring and Risk Management of Traditional Chinese Medicines

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Aim: To assess the overall safety of TCMs by analyzing the ADR monitoring data.
Methods: The ADR monitoring data of TCMs and that of chemical drug (2010–2012) were compared to make a preliminary assessment of the overall safety of TCMs.
Results: According to the ADR monitoring data of 2012, the number of ADR reports of TCMs is about one- fifth of that of chemical drug (17.1 %:81.6 %). The number of serious ADR of TCMs is about one-seventh of that of chemical drug (12.2 %:85.5 %). The ratio between serious ADR and ADR of TCMs is lower than the ratio between serious ADRs and ADRs of chemical drug (3.1 %:4.5 %) [1].
According to the 2012 annual drug sales data released by China's Ministry of Commerce, the annual sales of chemical drug were about 3.3 times of that of TCMs, and the amount of annual retail of chemical drug was about 1.3 times of that of TCMs. The ratio between the number of ADR reports of TCMs and that of chemical drug is lower than the ratio between the sales of TCMs and the sales of chemical drug [2].
Conclusions: The risk of TCMs causing serious ADR might be lower than that of chemical drug, but there are still certain TCMs that could result in serious ADRs, such as anaphylactic shock and drug-induced liver injury. Thus, it is necessary to carry out systematic safety studies and take appropriate risk management measures.
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Abstract Code: P-024

Update of Certolizumab Pegol Safety Profile: A Systematic Review and Meta-Analysis

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Introduction: Certolizumab pegol (CZP), is currently approved for treatment of Crohn's disease (CD), rheumatoid arthritis (RA), axial spondyloarthritis (AS) and psoriatic arthritis (PA) [1]. To our knowledge, no systematic review and meta-analysis, evaluating the overall safety profile of CZP in patients with immune-mediated inflammatory diseases (IMIDs), have been performed.
Aim: To assess the adverse event (AE) patterns of CZP versus control in patients with IMIDs, focusing on AEs, serious AEs (SAEs), adverse drug reactions (ADRs), infectious SAEs, injection site reactions, neoplasms and tubercolosis.
Methods: A systematic literature search was performed using PubMed/MEDLINE, EMBASE, Cochrane Library and FDA database for clinical

trials up to March 2014.Articles reporting randomized controlled trials (RCTs), evaluating the safety profile of CZP in patients with CD, RA, AS, PA or psoriasis, were selected for the meta-analysis. The following data were extracted: number and related incidence of patients who experienced overall AEs and SAEs, ADRs, withdrawals due to AEs, fatal AEs, infectious AEs, infectious SAEs, upper respiratory tract infections, injection site reactions, neoplasms (including malignant and benign lesions) and tubercolosis. Results were calculated as pooled risk ratios.

Results: A total of 2023 references were identified and a total of 18 RCTs, involving 6992 participants (4,589 randomized to CZP 200 or 400 mg, and 2,403 to control), were included. The main findings for the pooled risk ratios in CZP-treated versus control patients were: overall AEs 1.07 (95 % CI 1.03–1.10), overall SAEs 1.58 (95 % CI 1.31–1.92), overall ADRs 1.20 (95 % CI 1.05–1.38), infectious SAEs 2.14 (95 % CI 1.34–3.43), injection site reactions 2.01 (95 % CI 0.95–4.29), neoplasms 1.18 (95 % CI 0.59–2.39) and tubercolosis 2.90 (95 % CI 0.73–11.43). Risk ratios estimates for other safety data extracted in our study were: withdrawals due to AEs 1.19 (95 % CI 0.96–1.47), fatal AEs 2.08 (95 % CI 0.83–5.17), infectious AEs 1.21 (95 % CI 1.09–1.34) and upper respiratory tract infections 1.33 (95 % CI 1.15–1.53).

Conclusion: Safety data on CZP, largely originated from pre-authorization trials, suggest a favorable tolerability profile, with infections being the most common AEs. Large observational studies or the analysis of data from national registries of ADRs are needed, particularly for detecting rare AEs (such as neoplasms), that might occur after long-term exposures to CZP.

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Abstract Code: P-025

Characterization of the Risk of Bleeding with Novel Oral Anticoagulants and Warfarin: A Pilot Case-Control Study

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Introduction: A recent meta-analysis has shown a reduced risk of intracranial hemorrhage (ICH) and an increased risk of gastrointestinal bleeding (GIB) in patients with atrial fibrillation (AF) treated with novel oral anticoagulants (NOACs–dabigatran, rivaroxaban and apixaban) as compared with warfarin [1]. Little is known about the safety of NOACs in the real-life clinical practice.

Aim: To assess the risk of NOACs-related overall bleeding, and quantify the risk of ICH and GIB in patients with AF.

Methods: A monocentric, retrospective, case–control study was carried out to compare patients with AF, discharged from June 2013 to March 2014 from the Hospital of Lucca with a diagnosis of bleeding (cases) and non-bleeding conditions (controls). Cases and controls were matched for gender and age (±5 years) with a 1:2 ratio. The risk estimates are given as odds ratios (OR).

Results: The present analysis included 30 cases (13 males and 17 females; median age: 84.5 years; range 58–96) and 59 controls (26 males and 33 females; median age: 84 years; range 62–92). Both NOACs (OR = 14.25; 95 % CI 2.87–70.68; $P = 0.001$) and warfarin (OR = 2.71; 95 % CI 1.05–6.99; $P = 0.04$) were associated with an significant risk of overall bleeding. The risk of GIB was significant in patients treated with NOACs (OR = 21.00; 95 % CI 2.10–210.14; $P = 0.01$) and not significant in the warfarin group (OR = 0.53; 95 % CI 0.09–3.18; $P = 0.49$). By contrast, the risk of ICH was not significant in patients receiving NOACs (OR = 2.00; 95 % CI 0.12–34.82; $P = 0.63$) and significant in patients receiving warfarin (OR = 16.50; 95 % CI 3.06–89.06; $P = 0.001$). The univariate analysis showed a major distribution of risks factors for bleeding (treatment with medications that increase the risk of bleeding, etc) in the control group. However, owing to the small sample size, a logistic regression analysis to adjust ORs has not be performed.

Conclusions: This exploratory analysis showed that NOACs are associated with a significant risk of overall bleeding and confirmed a significant risk for GIB. The high OR estimated for NOACs as compared with that of the warfarin group might depend on a selective prescription (channeling) of NOACs to more susceptible patients. The preliminary results obtained in this study will address the development of a future multicentric study on a larger population.

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Abstract Code: P-026

Sampling Frame Stratification is Crucial in Evaluating the Effectiveness of Additional Risk Minimisation Activities (ARMAs)

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Background: Evaluation of ARMA effectiveness is mandated by European Medicines Agency (EMA) and other regulatory authorities. Recent regulatory changes, such as GVP XVI [1], has transitioned effectiveness from quasi market research (typically surveys and questionnaires of populations of interest), to more formal Post Authorisation Safety Studies (PASS) [2–3].

Aim: ARMA post-launch knowledge and behaviour evaluation are usually done on samples of prescribers and patients, but is susceptible to selection and response bias. We describe our experience in reducing biases by sampling frame stratification.

Methods: We reviewed results from four recent ARMA effectiveness evaluation PASS from 2013–2014, covering: oncology; metabolic; CNS; CVS indications; orphan and more commonly used medications. Each study represented a different approach to risk minimisation (RM), e.g. checklist, alert cards, registries. Effectiveness was interpreted from the

perspective of the RM tools process (i.e. distribution, coverage and comprehension/understanding). Outcomes indicators (changes in behaviour and response) were also examined [4]. Distribution and coverage of RM tools are aggregated by country, HCP specialism, patient age, gender and other demographic variables of interest.

Results: A typical randomised HCP sample/country was 480, of which 50 were recruited (assuming 50 % response rate CI 45.6–54.4) and 10 % incomplete survey rate. Differential product uptake can lead to non-representative samples. Inter-country variation in clinical practice may reflect HCP specialty and/or HCP type, and specific numbers of HCP. Small markets present a particular challenge, as statistically a greater proportion of prescribers and patients need to be recruited to maintain validity, but recruitment of greater than 10–20 % may be difficult to achieve leading to inadequate study numbers. Comparison of RM and behaviours of regular versus occasional prescribers is needed (Table 1), in addition to more generic demographics (e.g. time in professional practice). Similarly, patients of occasional and regular prescribers should be identified as these groups may receive differing amounts of risk education.

Conclusions: Appropriate stratification of representative sample frames of ARMA tool users is essential when designing evaluation effectiveness metrics. Persistent biases in sampling, including recruiting occasional prescribers, or detecting off label use, have led us to develop and implement RM tools that collect evaluation metrics in real-time [6].

Table 1 Attributes characterising regular versus occasional prescribers

Attribute	Range [5]
Total patients treated	1 to 50
Average number of patients treated/month	<1 to 10
Most recent patient treatment	≤1 to 6 months

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Abstract Code: P-027

Distinguishing Different Study Types, Biomedical Research, Market Research, Non-Interventional Studies and Clinical Trials: A Newly Developed Decision Tree

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In Europe a new guideline on good pharmacovigilance practices (GVP) 'Module II—pharmacovigilance system master file' was issued, came initially into effect on 2nd July 2012, with revision on 12th April 2013. The guideline describes in detail the Pharmacovigilance system master file (PSMF), which is a detailed description of the Pharmacovigilance system and supports/documents its compliance with the requirements. Establishing and maintaining a PSMF is a global activity. However, because of differences or absence of regulations, legislation or guidance documents (soft law) across the globe, definitions of studies may be different.

As part of the PSMF the marketing authorization holder in Europe should be able to produce and make available a list, including data arising from all study sources, the so called "study list", for inspection, audit and QPPV (qualified person responsible for pharmacovigilance) oversight. For medicinal products authorized in Europe this "study list" should describe, on a worldwide basis, the status of each study/programme, the applicable country(ies), the product(s) and the main objective. Most importantly, it should distinguish between non-interventional and interventional studies (clinical trials) and should be organized by active substance. The "study list" should include all ongoing studies/programmes as well as all studies/programmes completed in the last 2 years and may be provided as an Annex to the PSMF or separately.

There are distinct differences between biomedical research, market research, non-interventional and interventional studies, and a decision tree to support classification is proposed. This tool should improve harmonization of study assessment and minimise inter-country variability in the presentation of studies for the PSMF.

Abstract Code: P-028

Breast Discomfort in HIV Positive Patients Treated with Highly Active Anti-Retroviral Therapy

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Background: Benign breast discomfort has been reported as a very rare side effect in patients who are on highly active anti-retroviral therapy (HAART) for HIV infection. A 42-year-old Asian HIV positive male patient was admitted as an inpatient with left sided chest pain. A full history and examination revealed the tenderness was in the left breast and was not cardiac in origin, which was confirmed by investigations.

Aim: We conducted a survey to determine the prevalence of breast discomfort in our patient group.

Methods: 140 consecutive HIV positive patients seen between September 2013 and November 2013 by one consultant (P S Allan) were requested to complete a short questionnaire.

Results: 9/140 (6.4 %) confirmed they had breast discomfort during HAART treatment. There were 64 male and 76 female patients with an age range of 22–78 years (mean 43.5). The cohort consisted of 121 heterosexual, 16 men who have sex with men (MSM) and 2 bisexual patients. 57/140 (40.7 %) of patients were on atripla (tenofovir + lamivudine + efavirenz). The rest of the cohort were on various combinations of treatment.

Conclusion: Our study shows that breast discomfort is common among patients on HAART. None of the patients had serious breast diseases. The 3 male patients had mammograms with normal results in 2 patients; the third had a benign cyst which was then aspirated. The cytology was negative for malignant cells. The 6 female patients had various causes for the discomfort which are described in the table.

Discussion: We have analysed the spontaneous reports available on the Medicines and Healthcare products Regulatory Agency (MHRA) website for breast pain in patients treated with HAART [1]. There have been only 3 reports of breast pain, 2 with efavirenz and the other with lamivudine. Of our cohort, 69/140 (49.3 %) were on an efavirenz containing regimen. 7/69 (10.1 %) of these patients had breast tenderness, which suggests that this side effect is more common than previously reported. Two patients on other treatments reported breast tenderness—one on a regimen of lamivudine with nevirapine and abacavir, and the other on tenofovir, emtricitabine, darunavir and ritonavir.

Of the 9 patients with breast tenderness, 6 are female. Various causes can be attributed to their symptoms, such as previous H. zoster infection and menstrual pain. Further studies are required to identify the exact cause of breast tenderness in such patients.

Table

Age, sex	Treatment	Viral load	CD4 count	Comments
42, M	Atripla			Mammogram—normal
49, M	Atripla	69 copies/ml	550 cells/100 ml	Mammogram—cyst aspirated
55, M	Kivexa + Nevirapine			Mammogram—normal
39, F	Atripla			*H. Zoster* T5-7 in 2005
45, F	Kivexa + Efavirenz			On and off on the left side
45, F	Atripla			*H. Zoster* T4 left, no pain now
39, F	Atripla			Before periods
35, F	Atripla	156 copies/ml	130 cells/100 ml	Occasional breast tenderness
37, F	Truvada + Darunavir/Ritonavir			Mammogram—normal

Reference

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Abstract Code: P-029

Pharmacovigilance, Strategies for Implementation in an Emerging Country

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Background: Although Mexico is a member country of international pharmacovigilance program since 1999, it was not until recent years that the culture of safety during the medication begins to transcend and this much to the recent addition of Pharmacist at team health and active participation of the pharmaceutical industry. The Instituto de Seguridad Social del Estado de México y Municipios (ISSEMYM), public agency, decentralized, its functions are providing services designed to preserve, promote and maintain the health of more than one million beneficiaries. In its priorities include the timely and efficient supply of medicines and rational and safe use, reason for establishing the Institutional center in 2010.

Objective: Present strategies for the development of Institutionally Center of ISSEMYM.

Methodology: To develop institutional pharmacovigilance program is required the following activities: (1) Signing of an Agreement on Academic Cooperation between Institute and the School Pharmacy of the Benemérita Universidad Autónoma de Puebla (BUAP). (2) Professionalization of Pharmaceutical Services (Pharmacovigilance included). (3) Establish continuous surveillance criteria of drug safety in to the guidelines for public tendering and purchase contracts. (4) Diffusion of the NOM-220-SSA1-2012 Installation and operation of the pharmacovigilance [1], and promotion about importance of program aimed at patients and health team and promote voluntary reporting. (5) Intensive monitoring of those drugs reported as high risk or narrow therapeutic index.

Results and Discussion: As a result of the Academic Collaboration between BUAP and ISSEMYM it has been achieved professionalization of Pharmaceutical Services through recruiting Graduates in Pharmacy as well as the development of social service and professional practices of pharmacy students. The Pharmacists play an important role in the pharmacy and therapeutics committees, antibiotic control, clinical record, quality and pharmacovigilance, thus determining policy prescription drug use and acquisition.

Incorporation of Pharmacovigilance in the terms of competitive bidding and procurement of drugs and Regulation of Medical Services of the Institute [2]. Intensive monitoring of Oncology, biological and drugs documented failure or decreased effectiveness.

Conclusion: A few years after implantation of Pharmacovigilance in the ISSEMYM as Institutional Center, it has achieved a good level of response of the health team and the community, however it requires greater dissemination of the program and the conceptualization of it as an added value to the process of medication.

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Abstract Code: P-030

Dermatological Adverse Drug Reactions with Highly Active Anti-Retroviral Therapy

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Background: Highly active anti-retroviral therapy (HAART) has dramatically improved the life expectancy of HIV infected individuals. However, the same group of patients have a higher risk of developing cutaneous adverse drug interactions than the general population. Non-nucleoside reverse transcriptase inhibitors have been particularly implicated in adverse cutaneous reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome.
Aim: We report two HIV infected individuals with cutaneous adverse drug reactions associated with non-nucleoside reverse transcriptase inhibitors (nevirapine and efavirenz). We analysed the UK Medicine and Healthcare product Regulatory Authority (MHRA) yellow card data for cutaneous adverse events with these two drugs [1].
Case Number 1: A 36 year old South East Asian female diagnosed with HIV infection in 2005. Her HLA-B5701 was positive. She started HAART in 2006 with tenofovir, emtricitabine and efavirenz (Atripla) with a very good response. Her HIV viral load remained undetectable from November 2006, with her CD4 cell count gradually increasing to 620 cells/100 ml by January 2014. However, she had efavirenz-related significant central nervous system side effects, therefore efavirenz was changed to nevirapine in her treatment regimen. 4 weeks after changing treatment, she developed a sudden-onset, severe, extensive, erythematous macular rash starting on her chest and spreading to her face, back, upper arms and upper thighs. There was no mucosal involvement or history of haematuria. The positive findings of the investigation were her abnormal liver function tests (LFTs) with an ALT of 400 IU/L (10 × normal). Nevirapine was discontinued on the same day and the rash completely disappeared within 4 weeks, with her LFT returning to normal.
Case Number 2: A 47 year Caucasian male HIV positive patient was commenced on Atripla. He developed efavirenz related CNS side effects within 3 days of treatment. On day 7 he developed extensive, erythematous maculao popular rash starting on his chest and spreading to his back, upper arms and upper thighs. No other significant findings; investigations were normal. He continued his medication and his rash gradually got better over the next 4 weeks.
Conclusion: The number of Dermatological ADRs reported to the MHRA since the introduction of nevirapine and efavirenz are 316 and 194 respectively. We believe when a new medication is approved there should be a legal obligation for active reporting of ADRs. Healthcare professionals should have a profound knowledge of safety profiles of newly approved medications and actively report all adverse events to regulatory authorities to ensure patient safety.
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Abstract Code: P-031

Validation of Prescribing Errors Definition in Saudi Arabia

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Background: Few studies were conducted in Saudi Arabia to investigate the incidence of prescribing errors [1, 2]. Although a prescribing errors definition was validated in the United Kingdom (UK) [3], this definition need to be revalidated in Saudi Arabia to serve as a guide in studies evaluating the prevalence and incidence of prescribing errors within the general practice of Saudi Arabia.
Objective: To validate a definition of prescribing errors developed by a study in the UK.
Method: A definition of prescribing errors and 42 scenarios were evaluated by expert panel through a Delphi method. The judges were asked to indicate the extent to which they agree or disagree with the definition in a score of 1 "total disagreement" to 9 "total agreement" and were allowed to comment or suggest new definition or modify the given one.
Result: The study instrument was given to 35 judges. In the first round 31 (88.6 %) judges responded. In the second round only 24 (77.4 %) judges responded. Consensus was reached to accept the definition in the first round. For the scenarios of prescribing errors, consensus was reached to include 23 (54.8 %) scenarios in the first round. The remaining 19 scenarios were revaluated by the judges in the second round. Of these, consensus was reached to include 11, to exclude five scenarios and to include three scenarios depending on the individual clinical situation. Prescribing a drug without informing the patient of its uses and potential side effects, transcription errors and the use of inappropriate drug were included as prescribing errors. Prescribing against patient wish, deviation from national or treatment guidelines and prescribing by brand name were excluded.
Conclusion: Healthcare practitioner from Saudi Arabia agreed with the definition of prescribing errors developed in the UK with some minor modifications. However, it can be concluded that some types of prescribing errors might be considered as errors in Saudi Arabia but not in the UK. This definition could be utilized by future studies, in Saudi Arabia, and serve as a guide for future research on prescribing errors.
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Abstract Code: P-032

Pharmacovigilance at a University Hospital: Strategies Developed for Increasing Adverse Drug Reactions and Medication Errors Reporting

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Introduction: Prevention and minimization of the unintended effects of medicines is the main focus of pharmacovigiliance. However, analyze the causes of medication errors (ME) in hospital setting to identify and quantify the risks associated with the use of drugs should also be consider

an important part of a pharmacovigilance program. Underreporting of both, ADRs and ME is a well-documented problem in pharmacovigilance.
Aim: The objective of this study was to evaluate ADRs and ME at Hospital Universitario "Dr. José E González" in Monterrey, Nuevo León, México and discuss the effectiveness of strategies developed for increasing ADR and ME reporting.
Methods: The study was conducted, from January to December 2013. Several interventions: Educational activity, modification of ME reporting form, including computerized report, and implementation of a monitoring systems with feedback to the reporters were developed during 2013. The study was based on an analysis of spontaneous ADRs and ME reports and a comparison with 2012 reports. The parameters evaluated for ADRs, including: patient demographics, drug and reaction characteristics, and reaction severity and outcomes. For ME the type, consequences, and stage of medication process were the ME occurred were evaluated.
Results: An increase in the ADRs and ME reports was observed in 2013 with 61 ADRs and 349 ME reports vs 39 and 63 in 2012. The highest ADR rate was found in the adult age group 20–50 years and gender was not found to be a risk factor. The nurse team (80 %) reported the most ADRs. The most noticeable ADRs occurred in skin tissues, with such ADRs are more obvious to medical staff, with rashes being the most common reactions. The drugs responsible for most ADRs were vancomycin, carboplatin, docetaxel, ceftriaxone, and ciprofloxacin, 75 % of ADRs had moderate severity, thus requiring intervention. Most of the ME were in preparation process and were caused by missing actions. The most common types of error throughout the medication process were, dose and omission of drug/dose. A series of factors were considered responsible for ADR and ME underreporting, including knowledge, lack of time, respondents motivation and, attitudes.
Conclusions: In general the educational interventions and active surveillance of medication process improve the number of ADRs and ME reports. Further motivation and involvement of physicians to report ADRs should be consider. By understanding the causes of ME errors, the most appropriate interventions can be designed and implemented to minimize their occurrence.

Abstract Code: P-033

A Review of Allopurinol Hypersensitivity in Vietnam National Pharmacovigilance Database

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Introduction: Cases of allopurinol hypersensitivity documented has increased in line with the growing prevalence of gout nationwide. Allopurinol hypersensitivity is characterized by a variety of cutaneous reactions, including severe forms are rare but life-threatening.
Aim: This study was aimed at reviewing all case of allopurinol hypersensitivity in Vietnam National Pharmacovigilance Database and identify risk factors associated with developing allergic reactions.
Methods: All ADR reporting forms with allopurinol allergy during the period from January 2006 to December 2013 were collected. Severity of reactions were assessed by WHO toxicity grading scale for determining the severity of adverse events. Appropriateness of prescribing for allopurinol was judged according to Vietnam National Formulary. Proportional reporting ratio (PRR) was used for signal detection of severe cutaneous adverse reaction (SCAR), including Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), whose spectrum followed by the RegiSCAR project.
Results: A total of 56 ADR reporting forms, mostly from the Center of Allergology and Clinical Immunology, Bach Mai Hospital, which was specialized center for the treatment of drug allergy patients, were analysed. The common allopurinol dose was 300 mg (88.6 %), notably 2 patients having daily dose up to 900 and 1200 mg. Allourinol dose was not adjusted in 2 patients with renal failure. Inappropriate indications of allopurinol was 42.9 %, mainly patients with asymtomatic hyperuricemia. Rash and pruritus were the most common signs, however, dangerous generalized reactions, such as SJS and DRESS also remained high, 17.8 and 20.5 %, respectively. The majority of reactions (60.7 %) reached grade 4 of severity of skin or systematic reaction. As PRR was 45.3 (95 % CI 33.9–60.6), the signal of the relationship between allopurinol and SCAR was identified.
Conclusions: Irrational use of allopurinol (high-dose and inappropriate indication) suggested to be a risk factor associated with allopurinol hypersensitivity. It is of vital importance in adhering extensively to indications and dosages of allopurinol in the National Formulary to prevent adverse reactions. Strengthening spontaneous ADRs, including allergic reactions related to allopurinol in all hospitals nationwide was also proposed.

Abstract Code: P-034

Completeness Score of Individual Case Safety Reports in Vietnam National Pharmacovigilance Database

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Introduction: Individual Case Safety Reports (ICSRs) play a fundamental role in post-marketing surveillance. They permit provision of unexpected adverse reactions as well as helpful information in clinical practice. Over the last 3 years, the quantity of ICSRs in Vietnamese database has increased more than twice times. However, a comprehensive assessment on quality of these reports has not been previously undertaken.
Aim: To identify quality of ICSRs in Vietnamese database and related factors.
Methods: We performed a retrospective description study of the ADRs reported to the Vietnam National Center for the period from 2011 to 2013. VigiGrade which was a tool developed by Uppsala Monitoring Center was used to evaluate ICSRs. We classify reports with completeness score (C) > 0.8 as well-documented ones. Related risk factors including different primary reporters (physicians, pharmacists, nurses), level of health facilities in national health system and the ways to fill in ADR forms (e-reporting or handwriting) were considered as well.
Results: The results showed that among all the reported ADRs ($n = 10{,}856$), 71.1 % referred to well-documented ADRs ($n = 7{,}445$). The most frequently missing information field was dosage, indication, onset, and outcome. ADRs reported by pharmacist had higher quality than

physicians. ADR reports from central hospitals were identified at less completeness score compared to provincial and district hospitals. Using computer to fill in the reports provided better quality than handwriting.
Conclusions: This study has identified quality of ICSRs and factors that contributed to developing completeness score of ADRs reports in Vietnamese database. These data will be used for development of national training plan to promote ADR reporting system in Vietnam.

Abstract Code: P-035

Intensive Ppharmacovigilance in Outpatient of Internal Medicine in the Hospital Universitario De Puebla, Mexico

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Background: The main health problem in Mexico as in many parts of the world are chronic degenerative diseases [1]. Hospital Universitario de Puebla, medical unit of secondary care, has 39 specialties and subspecialties, 121 hospital beds and 52 non-census beds. Serves the BUAP workers (23,492) and their beneficiaries as well uninsured population [2]. Have an Institutional Pharmacovigilance Centre since 2001.
Objective: Develop the program of intensive pharmacovigilance in outpatients attending the clinic of Internal Medicine at the Hospital Universitario de Puebla, with the Pharmacist participation and identify risk factors.
Methodology: Prospective, descriptive, observational study including patients treated by one of the six physicians of Internal Medicine outpatient, who accepted the proposal for development of this work, from August 2012 to July 2013. Intern degree in pharmacy worked identifying possible adverse drug reactions (ADRs) and completing the official form designed for this purpose. Using independent sources, information of suspected drugs and potential drug interactions were analyzed. Information obtained was integrated to give an answer to the physician on the assessment of causality, severity (gravity), degree of information and type of reaction, using the guidelines established in the NOM 220-SSA1-2012 Instalación y operación de la Farmacovigilancia[3].
Results and Discussion: In the study period, 6,671 consultations were seen in the outpatient clinic of Internal Medicine. The participating physician attended 815 (12.2 %) consultations. 60 suspected ADRs were identified in patients with an age range between 24 and 93 years, with increased incidence 61–80 years and in females (62 %); The total of adverse reactions reported was 151, headache, nausea, pruritus, urticaria, abdominal pain, were the most frequently; Most drugs were reported: Metformina, lisinopril y lopinavir/ritonavir; being the causative drug metformin more reported and the diagnosis of diabetes mellitus and arterial hypertension are diseases with increased incidence in patients who experienced ADRs; Respect to gravity: 13 moderate, 45 mild, 2 severe; Causality: 39 probable, 21 possible. All patients receiving polypharmacy, this being higher in patients older than 60 years. A total of 173 drug interactions were identified, the majority (121) of moderate severity, being the most frequent: Acetylsalicylic/Sertraline acid and amiodarone/carvedilol. During study period no voluntary notification was received from other physician of Internal Medicine.
Conclusion: There is no adequate medical response to voluntary reporting, revealing the need for more training and dissemination of the National Pharmacovigilance Programme, involving the Pharmacist. The identified risk factors are advanced age and polypharmacy.
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Abstract Code: P-036

A Pregnancy Prevention Program for Revlimid® in China: Partnership between Company and HCPs

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Introduction: Celgene Revlimid® (generic name: Lenalidomide), a thalidomide analogue with a potential for inducing congenital malformations, was approved in China on 22 January 2013. As a condition for Revlimid® approval by China Drug and Food Administration (CFDA), a Pregnancy Prevention Program (PPP) was designed and implemented. The PPP primarily aims at mitigating fetal exposure through a closely controlled drug dispense program. The design and implementation of this program involves multiple stakeholders, including company and Healthcare Professionals (HCPs), i.e. prescriber, hospital pharmacy, retail pharmacy. A good partnership between the company and HCPs is the key for the success of this program.
Aim: Effective communication and training to advocate and encourage a partnership between the company and HCPs to maintain the effectiveness of the PPP.
Methods: In order to make the Revlimid® PPP a controlled distribution system that is both feasible and practical, stakeholders including physicians and pharmacists, were consulted at an early stage for their input. The finalized Revlimid® PPP design, was presented in several face-to-face training sessions with prescribers and pharmacists to provide transfer of knowledge and the associated PPP. Any instance of non-compliance to the PPP, was followed up with HCPs and appropriate corrective actions taken. Education of the principles of the PPP were also supported by an on-line presentation to support a much broader scope of physicians and further advocate the program requirements.
Results: Within the first year, 700 prescribers and 200 pharmacists were trained and registered in Revlimid® PPP. Only trained HCPs are entitled to prescribe and dispense Revlimid® in the designated controlled system. An extensive campaign of verbal and written communication directly supported the implementation. In addition, the online campaign of Revlimid® PPP reached a further 6,000 physicians in 148cities. The initial levels of compliance reflected the success of the company's effort to educate and familiarize the prescribers and pharmacists with the PPP. The additional

efforts of addressing instances of non-compliance also resulted in a gradual reduction of non-compliance associated with dispensing inconsistencies.

Conclusion: PPP implementation causes additional burden on the company and HCPs. Successful programs result when the burden is shared cooperatively between all stakeholders. Through continuous communication and advocation, the new concept of PPP is now better known and accepted by China HCPs. Revlimid® PPP continues to develop since its launch in May 2013.

Abstract Code: P-037

Sources of Disagreement between Investigator and Sponsor in Causality Assessment of Serious Adverse Events during Academic French Clinical Trials

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Background: In clinical trials (CTs), assessment of the relatedness of the research in the occurrence of a serious adverse event (SAE) is performed by both investigator and sponsor in accordance to French regulations and study documents.

Objective: To describe sources of disagreement between investigators and the sponsor (Bordeaux teaching hospitals) in causality assessment of SAEs during academic CTs.

Methods: All SAEs reported on year 2011 during academic CTs, with disagreement in causality assessment, were included in the study. For each SAE, causes of disagreement were reviewed by an event validation committee (two experts of pharmacology and clinical trial safety and vigilance).

Results: 48 SAEs with disagreement in causality assessment were identified among the 348 SAEs reported in 2011. For 32 SAEs (67 %), the sponsor presented arguments for the assessment: 10 SAEs (21 %) were possibly related to the research according to the investigator, but sponsor excluded a causal relationship since patients were in the control group; for 20 SAEs (42 %) the sponsor envisaged a causal link based on chronologic and semiologic criteria, while the investigator retained another cause (6 SAEs, 13 %) or did not specify any other cause (14 SAEs, 29 %); the investigator did not provide a causality assessment for 2 SAEs (4 %), which were considered as not related to research by the sponsor face to chronologic and semiologic criteria. For 16 SAEs (33 %), the sponsor retained a causal relationship with the research as it could not be excluded, while the investigator retained another cause for 9 SAEs (19 %) or did not specify any other cause (7 SAEs, 14 %).

Discussion: CT French regulations require that investigator and sponsor assess whether there is a reasonable possibility of a causal relationship between the research and the occurrence of SAE. Part of discrepancies may be explained by a lack of knowledge of investigator about CT regulations. In some cases, the investigator seems not to retain the research role when another cause exists and does not take into account a possible concomitant role of study. The sponsor concludes with arguments in most cases, but also retains the responsibility of the research if arguments to exclude it are missing even though the investigator describes another possible cause. A causality assessment method should be built for clinical trials in order to determine criteria and rules of assessment for both investigators and sponsor.

Abstract Code: P-038

A Signal Based on Spontaneous Reports of Convulsions in Association with Finasteride

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Introduction: The WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®, contains nearly 9 million ICSRs from 118 countries. VigiBase is managed by the Uppsala Monitoring Centre (UMC) and the data is routinely analysed in the UMC's signal detection process. As of December 2013, convulsions were reported in 34 ICSRs in association with finasteride, a 5α-reductase inhibitor used for the treatment of benign prostatic hyperplasia, androgenic baldness and female hirsutism.

Aim: Analysis of VigiBase ICSRs for an association between finasteride use and the subsequent development of convulsions.

Methods: Clinical review of all ICSRs in VigiBase of convulsions reported in association with finasteride.

Results: As of December 2013, VigiBase® contained 15 ICSRs of the WHO-ART term 'convulsions' and 19 ICSRs of 'convulsions grand mal' in association with finasteride. The ICSRs were submitted from the United States, United Kingdom, Canada, Germany and Italy. All patients but one were male and age, where reported, ranged from 19 to 84 years (median 49 years).Finasteride was considered the only suspected drug in 30 cases and was the only reported drug in 15 cases. Time to onset was reported in 17 cases and ranged from 6 days to 2 years (median two months). There were eight positive dechallenges, two of which were followed by positive rechallenge and one by negative rechallenge. One patient had a negative dechallenge. Confounders were identified in 15 cases and included epilepsy, concomitant drugs known to cause convulsions, non-adherence to anticonvulsant medications, high levels of alcohol and small vessel or white matter ischaemia.

Discussion: VigiBase contains 34 ICSRs of finasteride and convulsions, of which finasteride is reported as the only suspected drug in the majority of the cases. Some of the cases describe patients with predisposition to seizures and non-adherence to anti-convulsant medications. Recent studies have shown that endogenous neurosteroids may reduce seizure susceptibility in mice by enhancing the inhibitory effects of GABA and $GABA_A$ receptors [1–4]. Thus, reduced production of endogenous neurosteroids, by inhibition of 5α-reductase, may increase the potential for seizure activity. The development of seizures has been recorded in rats, with a permanently lowered seizure threshold, that were given finasteride in dose ranges comparable to human dosing [5].

Conclusion: A plausible mechanism together with cases presenting reasonable times to reaction onset and positive de- and rechallenges suggests that finasteride may cause increased seizure activity, particularly in susceptible patients with a history of seizures.

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Abstract Code: P-039

The Association between Oral Fluoroquinolone use and the Development of Retinal Detachment: A Systematic Review and Meta-analysis of Observational Studies

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Background: The findings of a study published by Etminan et al in 2012 has reported a potential association between the use of oral fluoroquinolones and retinal detachment among current fluoroquinolones users [1]. Several more observational studies were published since then but the findings are not consistent.
Aim: To investigate the association between the use of oral fluoroquinolones and the subsequent development of retinal detachment and estimate the overall absolute risk of such event among current fluoroquinolones users.
Methods: Literature search was performed using electronic databases (Pubmed, EMBASE and CINAHL) on the topic related to the association between oral fluoroquinolones and retinal detachment in May 2014. Studies with cohort, case–control and self-controlled case series study designs were included. Figures relevant to the measure of association between the use of oral fluoroquinolones and retinal detachment were extracted. Studies were narratively reviewed if they did not meet the criteria for meta-analysis. Cases of retinal detachment occurred during current fluoroquinolones use were extracted for absolute risk calculation.
Results: Six hundred and seventy-one citations were retrieved from the literature search and 7 of them were included in this study. Three of the included studies were meta-analysed and four studies (all of which were cohort studies) were narratively reviewed. A rate ratio of 1.82 (95 % CI 0.67–4.93), $P < 0.001$, $I^2 = 96$ % was estimated for the case–control studies and an incidence rate ratio of 1.03 (95 % CI 0.84–1.27), $P = 0.20$, $I^2 = 36$ % was found for the self-controlled case series studies. Three of the four cohort studies found non-significant association between oral fluoroquinolone use and the development of retinal detachment. The pooled absolute risk was estimated to be 4.85 per 1,000,000 prescriptions (95 % CI 0.78–8.91) among current fluoroquinolones users.
Conclusion: This systematic review and meta-analysis does not support the association between oral fluoroquinolone use and the development of retinal detachment. If there were an association between oral fluoroquinolones and retinal detachment, such event will be rare based on the low absolute risk. We should not alter the current prescribing practice based on the potential risk of retinal detachment.

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Abstract Code: P-040

ARV Toxicity Monitoring Using Targeted Spontaneous Reporting (TSR) Approach: Experiences from Vietnam

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Introduction: Despite of the fact that around 72,000 people living with HIV are receiving antiretroviral therapy (ART) in Vietnam in 2012, only 15 reports on ARV toxicity were received by National DI & ADR Center. Recently, WHO has developed targeted spontaneous reporting (TSR) approach which takes advantages and limitations from spontaneous reporting and active surveillance into account to improve quality of the reports. Vietnam has been chosen to pilot this approach for monitoring ARV toxicity while keeping unchanged workload for health staff.
Aim: To monitor and document AE among patients newly initiated or switched to TDF/3TC/EFV or TDF/3TC/NVP regimen by using TSR approach.
Methods: Renal and central nervous system (CNS) toxicity related to TDF and EFV were collected by doctors and nurses in all seventeen outpatient clinics (OPC) using a pre-qualified ARV reporting form. Reports from OPC were sent directly to the National DI & ADR Center. Feedbacks on the reports were sent back to OPC. Report on ARV toxicity was sent to the Provincial AIDS centre and Vietnam Authority for HIV/AIDS Control for actions if needed. The incidence of TDF-associated renal dysfunction, defined as more than 25 % decrement of estimated glomerular filtration rate (eGFR) from the baseline, was determined.
Results: By February 2014, 864 naived or treated patients, who switched from other ARV regimen to TDF/3TC/EFV or TDF/3TC/NVP regimen, were enrolled and followed-up. Mean age was 35.6 ± 7.5, 70.5 % patients were male, 28.9 % had CD4 $\geq$ 350, and 96.5 % used TDF/3TC/EFV regimen. 383 reports on adverse event (AE) were sent to National DI & ADR Centre. Number of patients experienced at least one EFV-related CNS toxicity was 373 (52.0 %). The most common five CNS toxicities were dizzy, tiredness, flush, headache and insomnia. CNS toxicity occurred mostly in the first month (93.3 %). Most of patients experienced minor AE (97.3 %) while severe AE occurred in 2.1 %. Regimen switching occurred in 19 patients of which 16 patients was due to ADRs. TDF-related renal dysfunctions occurred in 46 patients (13.2 %) and all of them experienced minor AE. Among then, 9 patients had eGFR < 50 ml/min/1.73 m^2.
Conclusions: TSR approach is feasible and could help documenting ARV toxicity by improving both quantity and quality of the reports. These preliminary experiences could be extended nationwide to support ARV toxicity monitoring in Vietnam.

Abstract Code: P-041

Pharmacovigilance and the Clinical Eye—Detecting New Drug-Induced Diseases

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Drug-related problems may develop in many different ways and situations. Adverse drug reactions and interactions are common and vary widely in nature and mechanism. Covering all this, in pharmacovigilance the early detection of new serious drug-induced diseases ("Type B adverse reactions") is of particular importance, and disasters such as thalidomide or practolol have been major reasons for maintaining the 'spontaneous reporting' system.

In the discovery of drug-induced diseases, clinical medical expertise plays a major role, both in signal generation and signal assessment. Bearing in mind the question "How surprised am I that this disorder occurs in this patient?", when assessing individual or small clusters of case reports a number of considerations matter:

1. Unexpectedness of the adverse event: clinically/pathologically unusual or unknown; low background frequency; unusual type of patient (e.g. age, sex); unusual disorder but known to occur with other drugs
2. No other obvious cause
3. Suggestive course of events (e.g. time relationship, outcome)
4. New drug
5. Pharmacological aspects
6. Unambiguous observation (one primary disease, one drug, one new disorder)

Physicians are explicitly requested or required to report observed suspected adverse drug reactions. In a reporting database serious adverse reactions are overrepresented, reports of established adverse reactions are common, and reporting bias may easily occur. Early signals regarding new drugs may consist of very small numbers of cases. Paradoxically in reporting databases signals regarding new adverse reactions to new drugs may be difficult to notice. In such situations medical knowledge may be helpful.

In the past decade many changes and improvements have been made in the study of medicines after their approval. In addition to these achievements, however, the countrywide system for ADR reporting by practising physicians will, in combination with judicious clinical assessment, continue to have an important early warning function in pharmacovigilance. This may be particularly true for new biopharmaceuticals and oncolytics with novel mechanisms of action.

Abstract Code: P-042

Towards Comprehensive Monitoring of Biopharmaceuticals

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Compared with "small molecule drugs", biopharmaceuticals are unusual if not extremely different. Likewise, effective pharmacovigilance of these medicines—"biopharmacovigilance"—may need modified or novel approaches. For example, biopharmaceuticals are typically very large molecules, immunogenic, administered parenterally and at large intervals, affect physiological processes at highly specific receptors often at subcellular levels, and are used for very specific and often rare diseases. All such features may have consequences for the development of adverse effects and for their monitoring.

We propose a scheme for the performance of biopharmacovigilance, which combines general clinical case reporting with targeted safety evaluation and pays attention to possibly expected as well as entirely unexpected problems. This approach takes into account a variety of characteristics; regarding the patient (disease treated and related morbidity, immune status, comorbidity), the drug (class, structure, immunogenicity, affinities, kinetics) and its use (route, dose, storage, co medication) as well as different types of adverse reactions to biopharmaceuticals.

This scheme may be helpful in planning a comprehensive evaluation of new biopharmaceuticals and allow for an early and safe introduction.

Abstract Code: P-043

Adverse Drug Reactions of Antiepileptic Therapy: A Retrospective Study in the Moroccan Pharmacovigilance Database

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Introduction: Adverse effects of antiepileptic drugs (AEDs) have a considerable impact on quality of life of people with epilepsy. They can lead to treatment failures in relation to early discontinuation of treatment, non-compliance with therapeutic doses and non-adherence to therapy [1, 2]. They can also be an important cause of disability, morbidity and mortality.

Aim: To describe epidemiological characteristics of adverse reactions to antiepileptic drugs reported in Moroccan pharmacovigilance data base.

Methods: We conducted a retrospective study of adverse drug reactions (ADR) related to AEDs reported in the Moroccan pharmacovigilance data base between 2005 and 2013. Causality assessment was performed by the WHO method. Statistical-descriptive analysis was performed.

Results: 288 Individual case safety reports (ICSRs) were collected between 2005 and 2013. The mean age of patient was 29.36 ± 21.94 years. Adults are mostly represented (51 %) and the women are more concerned (sex ratio = 0.86).70 % of patients take only antiepileptic drugs and 78 % showed one ADR. The most common ADRs described according to system organ class classification were Skin and appendages disorders (27 %), Central and peripheral nervous system disorders (19 %), Psychiatric disorders (13 %) and Body as a whole—general disorders (12 %).Valproicacid was the most suspected AEDs drug (23.6 %), followed by phenobarbital (19.5 %) and carbamazepine (17 %). The Causality assessment according to the WHO method revealed that the relationship was scored in 57 % as "possible", in 29.3 % as probable, in 6.5 % as "certain" or "improbable" and in 0.7 % there were no relationship. More than one third of the patients have serious ADRs. The outcome was favourable in 52 % and fatal in 2.6 % of the cases.

Conclusion: ADRs are most frequently observed with the first generation of AEDs (Valproic acid, carbamazepine and phenobarbital) probably in relation to their large prescription.

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Abstract Code: P-044

Effectiveness of Gastroprotective Agents on Prevention of Dabigatran Related Gastrointestinal Bleeding: A Population-Based Retrospective Cohort Study

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Introduction: An increased risk of gastrointestinal bleeding (GIB) in patients on dabigatran has been reported in randomized controlled trials and case reports; however, data on the concomitant use of gastroprotective agents is limited.

Aim: To examine the effects of gastroprotective agents on GIB in patients on dabigatran and identify risk factors associated with GIB.

Methods: Data were retrieved from the Clinical Data Analysis and Reporting System (CDARS), a database managed by the Hong Kong Hospital Authority who provides services to over seven million people in Hong Kong. Conditional logistic regression was applied to identify the risk factors of GIB and the effect of concomitant use of gastroprotective agents including proton pump inhibitors and histamine type-2 receptor antagonists, adjusted for patient characteristics and concurrent medications.

Results: Five thousand and forty-one patients prescribed dabigatran from 2010–2013 were included in the analysis. Of these, 177 (3.5 %) developed GIB during follow-up. Concomitant use of gastroprotective agents reduced the risk of GIB (OR 0.63, 95 % CI 0.44–0.90). Patients on concurrent statins were observed to have a lower likelihood of GIB (OR 0.52, 95 % CI 0.37–0.72). In contrast, those aged $\geq$ 75, with prior ischemic stroke, transient ischemic attack or systemic events, or a history of peptic ulcers or GIB were found to be at a higher risk of GIB.

Conclusions: Our study found that concomitant use of gastroprotective agents reduced the risk of GIB in patients using dabigatran. Additional research is warranted to confirm this finding. Detailed assessment on the interactions between gastroprotective agents and dabigatran is also encouraged to inform the risk-benefit profile of co-prescribing gastroprotective agents with dabigatran.

Abstract Code: P-045

The Unmet Needs of Antithrombotic Treatment in Patients with Non-Valvular Atrial Fibrillation in Real-World Clinical Practice

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Introduction: Antithrombotic treatment has been shown to be effective but underutilized in patients with non-valvular atrial fibrillation (NVAF). However, the management of NVAF patients is not well described in real clinical settings and among Asian patients.

Aim: To identify the proportion of undertreated AF patients; and to compare the risk of stroke and mortality among patients with good versus poor INR control in patients receiving warfarin.

Methods: Electronic records of patients newly diagnosed with NVAF during 2010–2012 were extracted from the Clinical Data Analysis and Reporting System (CDARS), a population database managed by the Hong Kong Hospital Authority who serves over seven million people in Hong Kong. Time in therapeutic range (2.0–3.0) $\leq$ 40 % was defined as poor INR control. Multivariate logistic regression was used to compare the risk of stroke and mortality within 1 year after receiving warfarin among patients with good and poor INR control, adjusted for age, sex and baseline morbidity.

Results: 30,238 new NVAF patients were identified in the database. Among the 17,801 (58.9 %) patients who had CHADS2 $\geq$ 2 (targeted group for anticoagulation), 3,422 (19.2 %) initiated oral anticoagulants (warfarin, dabigatran or rivaroxaban) and 10,242 (57.5 %) initiated only antiplatelet therapy (aspirin or clopidogrel) within 180 days after diagnosed with AF. In the subgroup analysis of 1,753 new warfarin users, 1,152 (65.7 %) had poor INR control. Results of logistic regression showed that patients with poor INR control were associated with higher all-cause mortality (OR = 1.50, 95 % CI 1.01–2.22) and a non-significant increase of the risk of ischemic stroke, transient attack or systemic embolism (OR = 1.25, 95 % CI 0.89, 1.75) compared to patients with good INR control.

Conclusions: In the real-life clinical practice, a large proportion of NVAF patients was not protected by anticoagulation or had suboptimal anticoagulation control. Poor INR control was associated with a significantly higher risk of all-cause mortality. Measures are needed to improve the underutilization and optimisation of anticoagulation in AF patients

Abstract Code: P-046

Risk Minimisation Actions within Pharmacovigilance Centres: Building a Public Health New Risk Minimisation Plan

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Risk management plan (RMP) including risk minimization actions is done in specific situations to oblige Marketing Authorization Holder to put in place actions intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur [1]. RPM is intended to ensure patient safety. Pharmacovigilance centres and public health care settings need to put in place Risk Minimisation Plans focused on public health in order to reduce harms and to improve patient safety.

Given the experience of the Moroccan Pharmacovigilance Centre (MPC) in Risk Minimisation Actions, the aim of our presentation is to highlight 5 Risk Minimization Actions done by the MPC and their impact on patient safety.

Through the Moroccan pharmacovigilance database, 5 signals leading to alerts have been detected. These triggered alerts concerned the Vitamin D and nephrocalcinosis in newborn, Metoclopramide and extrapyramidal syndrome, Methylergometrin and cardiovascular disorders, Flucloxacillin and tissular necrosis and Paracetamol in children and hepatic troubles.

Method used for each detected alert is the root cause analysis using the Ishikawa diagramme [2] in order to look for contributing factors leading to preventable ADRs occurrence. Contributing risk factors identified are associated to methods used as regulations, procedures and protocols, to patients and relatives, to the medicine used and to health care professionals.

Risk Minimization Actions taken towards alerts concerned regulation actions involving the Moroccan Health Authority and Marketing Authorization Holders with changes in recommended doses, in posology, in the patient package insert and medicine packaging, in principles of prescribing and dispensing medicines.

Risk Minimization Actions taken focused on sensitization and information of health care professionals on rational use of these medicines and also focused on education and trainings patient and relatives on risk of selfmedication.

Following these different actions, the number of these preventable adverse drug reactions decreased.

Pharmacovigilance centres should reinforce their roles around Patient Safety objectives and should build Risk Minimization Plan to systemize risk minimization actions for public health settings in order to complete the one done by marketing authorization Holders and then there is a need of guidance on how to do.

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Abstract Code: P-047

Implementing the Moroccan Database by an Automated Signal Detection Method

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Introduction: The signal detection (SD) is a key pharmacovigilance activity carried out in national competent pharmacovigilance centres. Currently, there are no universally applied signal detection methods or agreed standards. In our experience, until 2013, the detection of signals was performed based on a quarterly review of individual case safety reports ICSRs which generates many potential signals. These hypothesis usually led to quantitative analysis which measure the disproportionality for the signal strengthening. Recently, pharmacovigilance centres devoted considerable efforts to develop and implement computer-assisted automated signal detection methodologies that employ statistical theory to enhance screening databases of spontaneous reports of adverse drug reactions (ADRs).

Objective: The aim of our study is to set up an automated SD in order to identify early signals in our database.

Materials and Methods: It was a retrospective analysis of our database from January 2004 to December 2013. A total of 10886 ICSRs were extracted from "vigiflow", from which we excluded 2967 ICSRs originated from literature.

The 7919 selected ICSRs, corresponded to 150821 couples of health products/adverse reactions .For data harmonization, the adverse reactions were coded into WHO art terminology preferred terms and for the drugs we used the INN. We applied the reporting odds ratio (ROR) to evaluate the disproportionality for each couple, the statistical significance level was set at ROR ≥ 2, Chi square ≥ 4, the number of individual cases ≥ 3 and the lower confidence(IC) limit of the ROR is ≥ 1 [1].

Results: Among the selected ADRs/Health products couples, 80 % concerned medicines, 11 % were related to vaccines and 9 % to plants.

The most common labeled signals detected in our database were: stevens johnson syndrome/allopurinol [ROR = 34.4, 95 % CI (17.5–67.5), $\chi^2 = 267.15$], epidermal necrolysis/ allopurinol [ROR = 19.9,95 %CI (9.7–40.9), $\chi^2 = 131.5$]; extrapyramidal symptoms/metoclopramide [ROR = 271, 95 % CI (180–406), $\chi^2 = 4494.06$]; Steven Johnson syndrome/sulfamethoxazole-trimethoprim/[ROR = 6.38, CI 95 % (2.8–14.8), $\chi^2 = 24.68$]; epidermal necrolysis/sulfamethoxazole-trimethoprim/ [ROR = 6.4, CI 95 % (2.8–14.8), $\chi^2 = 24.7$].

The unlabelled potential signals detected were related to medicines (lower limb oedema /antituberculosis drugs), plants (embryopathy/ *Trigonella Foenum* Graecum). These signal were not yet validated.

Conclusion: Although the automated SD methods were criticized regarding the biased interpretation. They can generates statistical values which alert safety evaluators for potential safety issues and actual safety signals.

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Abstract Code: P-048

There is Geographic Variation of the Frequency and Profile of Adverse Drug Reactions—An Analysis for Tyrosine Kinase Inhibitors

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Background: Different population characteristics, co morbidities and co medications may result in different ADR profiles and frequencies across countries. Although such differences might have an important impact on risk minimisation activities there are few empirical data on and little interest in the geographic variation of adverse drug reactions (ADR).
Objectives: We aimed to find out whether the profile of ADRs of the TKI imatinib used to treat chronic myeloid leukemia indicates geographic variation.
Methods: The literature search in English used the following key words: imatinib, adverse event, ADR, safety, prospective study, CML. All prospective studies with adults who received 400 mg/day imatinib were included if they provided quantitative data on ADRs. ADRs were grouped using the SOCs of the WHO. ADR profiles were constructed by calculating the relative frequencies of the SOCs for each study.
Results: We identified 13 studies, representing patients from Europe, Asia (Japan and India) and the USA with 2,424 CML patients from 13 countries. The ADRs reported were classified in 16 SOCs. Seven SOCs were reported most often: body as a whole - general disorders; GI system disorders; muskulo-skeletal system disorders, platelet, bleeding and clotting disorders; red blood cell disorders, skin and appendages disorders; white blood cell and reticuloendothelial system disorders. These SOCs showed similar relative frequencies except for skin and appendages disorders, which were reported more frequently in Asia than in Europe and the USA. Differences were seen too for ADRs of the cardiovascular and the central nervous systems, both were reported more often in Europe and in the USA. ADRs which were reported more often in Asia than in Europe and the US were liver, biliary, and urinary system disorders. Metabolic and nutritional ADRs were reported in Europe and the USA only. Vascular (extra cardiac), and special senses ADRs were reported in Asia and Europe only.
Conclusions: There was considerable geographic variation concerning frequencies and profiles of ADRs in eight different SOCs between Asia, Europe and the USA. Our results thus indicate that there is considerable geographic variation of drug safety issues which deserve more attention.

Abstract Code: P-049

Monitoring the Safety of Mass Measles and Rubella Immunization Campaign in Morocco

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Introduction: In accordance with World Health Organization recommendations to eliminate measles, rubella and congenital rubella syndrome (CRS) altogether by 2015, in 2013, a National Mass Measles and Rubella (MR) immunization Campaign in Morocco occurred among subjects aged from 9 months to 19 years. More than 11,179,000 children are expected to be immunized between 24 April to 20 May 2013.
Aim of the Study: To document and evaluate the safety of MR vaccine used during the immunization campaign, to determine the incidence of adverse events in the vaccinated population targeted and to classify all events observed according to WHO categories AEFIs As defined by (CIOMS/WHO 2012).
Methods: During the MR campaign, the Centre Anti Poison et de Pharmacovigilance du Maroc conducted a reinforced monitoring programme. This was based on a stimulated spontaneous reporting system until six weeks after MR immunization.
Results: In Morocco, over 10,191,571 doses of measles and rubella vaccines (Indians Laboratories) were administered to children aged 9 months to 19 years and 480 adverse event case reports were submitted, representing a reporting rate of 4.7 per 100,000 doses.
According to Cause–specific categorization of AEFI (CIOMS/WHO 2012), 49 % events were related to vaccines product, 44.3 % related to immunization anxiety, 4.5 % to immunization error and 1.5 % were coincidental events.
Among 729 events reported, the most commonly reported adverse events were neurologic events (236 cases), gastro intestinal reactions (156) and allergic reactions (94),
36 case reports described as serious (0.4 per 100,000 doses) with hospitalization for all cases included 5 cases of thrombocytopenia, 3 of polyradiculonevritis, a case of anaphylaxis and 1 of acute disseminated encephalomyelitis. Of the 36, 19 % were considered probably or certainly related to vaccination.
Five episodes of mass hysterical illness occurred among clusters of schoolchildren in several provinces during the campaign. Assessment of the episodes concluded these were hyperventilation syndromes brought on by anxiety
Conclusion: MR vaccines are very safe, and adverse events are minor, especially when compared to diseases they are designed to prevent. Surveillance allows program to detect abnormalities in the vaccine or program errors. This is of utmost importance during vaccination campaign measles-rubella supplementary immunization activities, when a large number of doses are administered in a short time.

Abstract Code: P-050

High-dose Methotrexate: Drug–Drug Interaction and Toxicity

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Introduction: High-dose Methotrexate (MTX) is used in the treatment of a variety of solid tumors and haematological malignancies. MTX is eliminated primarily via renal excretion; hydratation and urine alkalinisation prevent severe intoxication. Despite these measures, delayed elimination and acute renal failure occur in 1.8 % of cases [1]. The rescue agent used is carboxypeptidase G2. Severe intoxication can be facilitated by co-administered drugs such as anti-inflammatory drugs, penicillin and proton pump inhibitors (PPIs).
Aim: To evaluate the potential implication of co-administrated drugs in patients treated by carboxypeptidase G2 for severe MTX toxicity.
Methods: We reported a retrospective non-interventional study with all cases of high-dose MTX intoxication requiring the administration of carboxypeptidase G2, occurring at the University Hospital of Nantes, France, between 2005 and 2013. Various criteria were taken into account for analysis: epidemiological data of the patient, co-administered drugs, MTX plasma level and renal function. Assessment of drug–drug interaction with MTX is based with mention in the summary of products characteristics and literature data.
Results: Ten patients (5 adults and 5 children) were identified with an administration of carboxypeptidase and we suspected an interaction with MTX in seven of them: 6 times with PPI. The other drugs were valaciclovir, penicillins, furosemide and morphine. In 5 patients, many of these drugs were associated.

Conclusions: Several mechanisms are reported to explain MTX intoxication with concomitant use of drugs. Anti-inflammatory drugs and penicillins are known to inhibit the transport of MTX via the organic anion transporters (OAT). Some hypothesis have been proposed for PPI-induced interference with MTX: PPIs inhibit renal H +/K + ATPase which supports the active tubular secretion of MTX resulting in an increased half-life of MTX [2], or the inhibitory effects of PPIs on BCRP-mediated MTX transport [3]. In some patients, the association of several drugs are known to interact with MTX therapy and may result in an increased risk for MTX toxicities. Some patients in our study have no co-administered drugs and drug interactions cannot be explain solely all of the intoxication cases. Polymorphism genetic may affect substrate affinity to multiple efflux pumps and to OAT.

We encourage reporting of suspected cases of drug–drug interactions to the pharmacovigilance center. Physicians should bear in mind the possibility of drug–drug interaction with high-dose MTX, may be these precautions should extend to patients taking low-dose MTX.

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Abstract Code: P-051

Acute Pancreatitis after Morphine Sulfate Ingestion: Report of Two Cases

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Background: Acute pancreatitis is a serious medical condition with considerable morbidity and mortality. A variety of drugs has been reported to cause this adverse effect during the past 40 years and several reports of acute pancreatitis due to codeine ingestion have been notified for over 10 years.

Aim: Reminder of acute pancreatitis after morphine sulfate ingestion in young patient.

Observation: We report two cases of acute lipase increase associated with morphine sulfate administration. The first case concerns a twelve-year-old female with a medical history of asthma. She was hospitalized after a horse fall that caused a finger fracture and luxation. She was treated with morphine sulfate on the 23th of July, 2013 and rapidly developed an acute pancreatitis (lipase: 2226 UI/l [37 N] (normal value: 0–60 UI/l) related to a severe epigastric pain. The outcome was favorable in 24 h, with a lipase decrease up to 116.4 UI/l. The second patient is a thirteen-year-old male with no medical history. He was treated with morphine sulfate on the 27th of June, 2013 in the context of an ankle trauma. He developed a pancreatitis (lipase: 950.4 UI/l) [16 N], with a rapid normalization in 24 h (99 UI/l). In both cases, other origins of acute pancreatitis such as hyperlipidemia, hypercalcemia or previous cholecystectomia were excluded and both patients were treated with therapeutic doses for a trauma.

Discussion: Since codeine undergoes metabolization via cytochrome P450 enzyme system (isotype 2D6), to become active morphine (10 %), toxicity of codeine could be translated to morphine. It is known that ingestion of therapeutic doses of codeine (or morphine) may result in rapid constriction of the sphincter of Oddi that lasts approximately 2 h. In our cases, morphine would be an accelerating factor for several reasons. First, a close temporal relationship between drug ingestion and the onset of symptoms and then, a rapid relapse confirmed biochemically were observed. Second, extensive investigations including bile sampling and routine blood tests enabled the exclusion of other known causes of pancreatitis. [1–3]

Conclusion: Patients should be carefully monitored for acute lipase increase after opiate prescription. The pathophysiological mechanism involves probably spasm of the sphincter of Oddi. Morphine, similarly to codeine should be considered as a cause of acute pancreatitis, and this information should be harmonized in the French Summary Characteristics Products of Morphine and its derivatives.

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Abstract Code: P-052

Drug-Induced Anaphylaxis Monitored in A Tertiary Teaching Hospital in South Korea

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Introduction: Drug induced anaphylaxis is potentially fatal drug hypersensitivity; especially when presenting as an anaphylactic shock. Because drug induced anaphylaxis is unpredictable and abruptly after exposure to causative drug, initial management is critical.

Aim: The purpose of this study is to investigate clinical characteristics of in-hospital drug-induced anaphylaxis and appropriateness of anaphylaxis treatment.

Method: We retrospectively reviewed the medical records of 146 adult cases of drug-induced anaphylaxis reported to the Seoul National University Hospital Pharmacovigilance system between September 2009 and June 2013.

Result: The mean age was 58.00 ± 1.11 (SEM) years and 47.3 % (69 cases) were male. The most frequently involved organ was skin (81.5 %), followed by respiratory (74.0 %) and cardiovascular (69.9 %) systems. The most frequent causative drug was anticancer drug (43.8 %) followed by radiocontrast media (33.6 %), antibiotics (8.9 %), muscle relaxant (5.5 %). Antihistamine (87.7 %), steroid (74 %) and epinephrine (34.2 %) were used for anaphylaxis treatment and only 11.1 % among patients with respiratory symptoms were used bronchodilator. Anaphylactic shock, with symptoms of hypotension, occurred 65.8 % of total anaphylaxis patients. Muscle relaxant (100 %) and radiocontrast media (87.8 %) more frequently developed anaphylactic shock than anticancer drug (48.4 %) and antibiotics (61.5 %). Among patients with anaphylactic shock, epinephrine was used 42.4 % of ward patients, 53.5 % of outpatients and 75 % of

operative room patients. Following drug classification, epinephrine was more frequently administered in cases induced by antibiotics (75 %), muscle relaxant (75 %), and radiocontrast media (62.8 %) compared to cases related with chemotherapeutic agents (25.8 %).

Conclusion: Anticancer drugs were major causative agents of drug induced anaphylaxis. Muscle relaxant and radiocontrast media were more frequently developed of anaphylactic shock. Management of anaphylaxis was affected developed location and drug classification. Education and promote is needed to the proper management of anaphylaxis.

Abstract Code: P-053

Chemotherapy-Induced Thrombocytopenia: Frequency and Relative Risk in Cancer Patients in Tertiary-Care Hospitals in Malaysia

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Introduction: Thrombocytopenia is a common treatment-related adverse event (AE) and dose-limiting toxicity for various chemotherapy regimens. [1–5] Till today, very few studies are conducted to examine frequency and relative risk (RR) of chemotherapy-induced thrombocytopenia (CIT) in adult cancer patients of solid tumours receiving chemotherapy.

Aim: To estimate the frequency and RR of thrombocytopenia in adult cancer patients receiving chemotherapy for solid tumours in Malaysia.

Methods: A retrospective, hospital-based study was performed onadult cancer patients having solid tumours who treated with chemotherapy in past 3 years at tertiary hospitals in Malaysia. For this study, frequency of overall thrombocytopenia, frequency of isolated thrombocytopenia and the frequency and RR of overall thrombocytopenia and isolated thrombocytopenia associated with different cytotoxic agents were examined. All obtained data were analysed using descriptive and inferential statistics.

Results: Among total of 468 patients, the frequencies for overall thrombocytopenia and isolated thrombocytopenia were 47.7 % and 24.6 % respectively. For overall thrombocytopenia, highest frequency was observed in patients receiving carboplatin monotherapy (68.3 %) than for patients receiving combination therapies i.e. carboplatin, gemcitabine, etoposide and paclitaxel. For isolated thrombocytopenia, the highest frequencies were noted with combination therapies comprising oxaliplatin (44.4 %) and gemcitabine (39.1 %). For both overall and isolated thrombocytopenias, the highest RRs (compared with cisplatin-based therapy) were observed for combination therapies.

Conclusions: The results of this study suggest that CIT is a pertinent problem in clinical practice. Our data suggested that a potential pre and post chemotherapy dosing scheme should be adopted and strictly followed in patients experiencing chemotherapy-induced thrombocytopenia. The observed immune-mediated thrombocytopenia due to oxaliplatin and gemcitabine further strengthen the suspicion that these drugs cause immune-mediated thrombocytopenia. Further research is needed to investigate the clinical consequences of thrombocytopenia in cancer patients receiving chemotherapy.

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Abstract Code: P-054

Pioglitazone and Risk of Bladder Cancer Among Type 2 Diabetic Patients: A Malaysian Perspective

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Introduction: Earlier studies have suggested that long-term exposure to pioglitazone increases the risk of bladder cancer however the exact mechanism of this association has not been finalized. Few studies had been conducted to find out association of bladder cancer with long-term exposure to pioglitazone. However, such work has not been previously undertaken in Malaysia.

Aim: This study was aimed to investigate the potential risk association between pioglitazone exposure and bladder cancer in adult patients with type 2 diabetes in tertiary care hospitals in Malaysia.

Methods: A retrospective, hospital-based study was performed ontype 2 diabetic adult patients who were ≥35 years of age and admitted in past 3 years at tertiary hospitals in Malaysia. Patients with prior bladder cancer were excluded from this study. For this study, pioglitazone exposure (dose and duration) was taken as a time-dependent variable and defined by having filled at least two prescriptions over 6 months. All obtained data were analysed for various parameters like multivariate cox regression model (Hazard Ratios) adjusted for various variables like age, sex race, HbA1C, heart failure, income, renal function and other glucose-lowering drugs, using descriptive and inferential statistics.

Results: A total of 79 cases of bladder cancer were found among 600 exposed patients. Pioglitazone exposure was moderately associated with bladder cancer incidence (adjusted HR 1.03 [95 % CI 1.01–1.62]). A higher risk of bladder cancer against high cumulative doses and significantly highest risk of bladder cancer in long duration of exposure of pioglitazone (≥2 years, adjusted HR 1.22 [1.02–1.84]) were observed.

Conclusions: The results of this study suggest that high dose exposure to pioglitazone was associated with higher odds of bladder cancer whereas long-term exposure (≥2 years) was associated with the highest odds of bladder cancer among patients with type 2 diabetes.

Abstract Code: P-055

Quantitative Benefit-Risk Assessment of Rosiglitazone: Number Needed to Treat, Number Needed to Harm and Likelihood to be Helped or Harmed

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Introduction: The cardiovascular (CV) safety of rosiglitazone have been discussed since the publication of a meta-analysis of RCTs that demonstrated an increased risk for myocardial infarction (MI) and CV death. [1] While European Medicines Agency (EMA) decided to withdraw rosiglitazone from the market in 2010, [2] Food and Drug Administration (FDA) kept the drug in the market and further recently voted to ease the current restrictions. [3]
Aim: To quantitatively assess the benefit versus risk for rosiglitazone by the calculation of the likelihood to be helped or harmed (LLH).
Methods: Efficacy data was retrieved from RCTs supporting the marketing authorization application of rosiglitazone. [4] The efficacy outcomes were the rate of HbA1c and fasting prandial glucose (FPG) responders. HbA1c and FPG responders were defined as patients who had $\geq$0.7 % and $\geq$30 mg/dL decrease from baseline in HbA1c and in FPG, respectively. The number needed to treat (NNH) and its 95 % CI was calculated for each efficacy outcome. Safety data was retrieved from a FDA meta-analysis of RCTs (versus placebo or non-thiazolidinedione anti-diabetics, i.e., metformin, sulfonylureas) between 2 months and 2 years in length with targeted total daily dose of 4 or 8 mg of rosiglitazone. [5] The safety outcomes were major adverse cardiovascular events (MACE), CV death, MI, stroke, all cause death, serious myocardial ischemia (MIS), total MIS, and cardiac heart failure (CHF). The number needed to harm (NNH) and its 95 % was calculated for each safety outcome. LLH was calculated as NNH/NNT ratio for each outcome for placebo-controlled trials (PboCT) and active-controlled trials (ActCT) if NNH had been found to be statistically significant.
Results: 38 PboCT and 14 ActCT (including 12425 and 5350 patients, respectively) were included. NNT was estimated at 3 (CI95 %: 3–4) for HbA1c responder and at 3 (CI95 %: 2–3) for FPG responder in PboCT. Statistically significant NNH were found for serious MIS (266; CI95 %: 144–1736), total MIS (180; CI95 %: 100–944) and CHF (241; CI95 %: 139–902). LLHs were estimated at 87 for serious MIS, 60 for total MIS and 80 for CHF irrespective of the efficacy outcome since both have the same NNT. Statistically significant NNHs were not found in ActCT and therefore LLHs were not estimated.
Conclusion: Rosiglitazone was associated with an increased risk of CV adverse events versus placebo, but not versus active comparators. Additional research is needed to provide further data on the comparative CV safety of rosiglitazone versus other thiazolidinediones.

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Abstract Code: P-056

Urinary Diamonds with Perioperative Prophylactic Amoxicillin: A Regional Investigation to Define Causes and Prevent Further Cases

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Introduction: Suspected cases of amoxicillin-induced crystalluria were reported in our hospital in 4 women during bariatric (2) or gynecologic surgery (2). Cases were severe due to acute renal failure although reversible. The symptoms were a transient hematuria and/or oliguria and acute renal failure following the surgery, soon after the administration of amoxicillin/clavulanic acid in perioperative prophylaxis. Several cases have been described after a high dose of amoxicillin intake [1–4] but only 3 cases after neurosurgery antibioprophylaxis.
Aim: The aim of our study was to describe and analyze all cases of crystalluria occurring in theParis area after prophylactic use of amoxicillin during surgery in order to avoid new cases.
Methods: All renal adverse effects with amoxicillin reported in theParis area from 2010 to May 2014, were reviewed and the cases of crystalluria in the perioperative setting were retained.
Results: The French national database of pharmacovigilance query found 34 cases of acute renal failure in perioperative antibiotic prophylaxis with amoxicillin/clavulanic acid reported in our area. Twelve cases occurred during in digestive surgery, in 9 women, 3 men; symptoms were oliguria (83 %), hematuria (50 %), 4 macroscopically crystalluria, 3 confirmed by urinalysis. Sixteen in urogenital surgery, (15 women, one man); symptoms were oliguria (75 %), hematuria (69 %), one macroscopically crystalluria, 2 cases without oliguria or hematuria. Six unknown surgery (4 women, one man, one sex unknown); sympoms were oliguria (83 %), hematuria (83 %), 6 macroscopically crystalluria, 5 confirmed.
Conclusion: In these patients, regarding the short time period between administration and symptoms, we diagnosed crystalluria, a direct toxicity on tubular kidney rather than drug hypersensitivity. Amoxicillin crystalluria is favoured by reducing the drug solubility in the urine such as acidified urine, low diuresis, plasma peak due to fast injection. The observation of non-metabolized needles sheaf of amoxicillin tri-hydrate

crystals in urine is the only way to confirm the diagnostic of amoxicillin-induced crystalluria. Some cases are only suspected because the urinalysis could not be performed on time systematically. We noticed that the first cases of these adverse effects are notified since 2010 after a change in antibiotic prophylaxis guidelines by the French society of anesthesia [6]. Two cases show neither oliguria nor hematuria suggesting an under-reporting and showing only the tip of the iceberg. New guidelines concerning amoxicillin administration during surgery will be transmitted in the next weeks.

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Abstract Code: P-057

Digoxin Dosing and Monitoring in Hospitalized Patients

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Background: Digoxin has a narrow therapeutic range and significant side effects. The therapeutic range has changed over the years. Currently a lower range than previously recommended is advised (0.5–1 ng/ml compared 0.8–2 ng/ml). Yet, there is no uniformity in the accepted and used therapeutic ranges in health systems. Physicians' proficiency regarding dose adjustment and monitoring of digoxin is lacking.

Aim: Assessment of digoxin dosing and monitoring in hospitalized patients.

Methods: A retrospective review of the records of hospitalized adults treated with digoxin and tested for digoxin serum levels, during a period of 25 months (October 2010–October 2012).

Results: During the study period 764 adult patients were treated during hospitalization with digoxin. Patients were hospitalized in 18 different departments. New digoxin loadings were performed in 272 (35.6 %) patients. Regarding maintenance dosing, 598 (78.3 %) patients received doses of 0.125 mg, 166 (21.7 %) patients received doses of 0.25 mg and one patient was treated with doses of 0.0625 mg. Digoxin was administered on a daily basis in 613 (80.2 %) patients; the remainder were not treated every day. Approximately two-thirds of patients (478, 62.6 %) were tested for digoxin serum levels during their hospitalization; some were sampled multiple times. A total of 935 samples were tested out of which 392 (42 %) samples were in the range of 0.5–1 ng/ml; 315 (37.4 %) samples were in the range of 1.1–2 ng/ml. A quarter of the samples were outside any therapeutic range, past or present (226, 24.1 %); 134 (14.3 %) samples were below 0.5 ng/ml and another 92 (9.8 %) over 2 ng/ml.

Conclusion: digoxin therapy is common in hospitalized patients in various departments including new treatment initiations. Only half of the patients were tested for the medication serum level during hospitalization. Many patients were not controlled on the current recommended therapeutic range. There is a need to set an updated and unified therapeutic range and clear clinical guidelines for digoxin dosing and monitoring. Pharmacovigilance measures are necessary to improve digoxin treatment.

Abstract Code: P-058

Global Risk Management Systems? Process and Methodology to Achieve an Applicable Framework

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Introduction: The objective of a product's benefit-risk management plan is to ensure that benefits exceed the risks of harm by the greatest achievable margin. However, the scope of the risk-management system needs to be both proactive and globally applicable to standardise and adapt to the global diversity of patients and local health care systems. The majority of countries in the Asian-pacific region have not released clinical risk management system guidance. Therefore, the European good pharmacovigilance practices (GVP) guidance[1,2] related to risk management provide a logical framework to develop globally applicable risk management plans. Integrating global diversity into risk management systems requires an adaptable methodology to provide the rationale for the characterisation of clinical risks. To overcome this challenge, Global Safety in Novo Nordisk has chosen to use 'Failure Modes, Effects and Criticality Analysis (FMECA)' methodology to support the characterisation of clinical risks.

Aim: To describe how Novo Nordisk develops globally applicable and proactive risk management systems based on health authority guidance coupled with the thorough characterisations of safety and efficacy concerns and to explain how this process can be adapted to evaluate and propose appropriate benefit-risk management across the Asia-Pacific region.

Methods:

1. Describe strategies how to use the European GVP risk management system guidance to develop globally applicable risk management plans at various lifecycle stages
2. Describe the use of FMECA to characterise safety and efficacy concerns in global health care systems and how this supports pharmacovigilance and risk minimisation planning

Conclusion: The risk management plan developed using the European guidance is useful for supporting global clinical risk management planning. Appropriate, globally adaptable characterisation of safety and efficacy concerns provides the focal points for targeted pharmacovigilance and risk minimisations, which helps optimise the benefit-risk balance of the product throughout its lifecycle.

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Abstract Code: P-059

Adverse Events Associated with Canagliflozin Mechanism of Action: A Meta-Analysis of Randomized Clinical Trials

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Introduction: Vulvovaginal mycotic infections and urinary tract infections (UTIs) are common complications in women with diabetes, in particular when there is a poor glycemic control and glucosuria. [1,2] Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor developed to treat type 2 diabetes (T2-DM), acts by increasing urinary glucose excretion (UGE). [3] Additionally, the mechanism of action of SGLT2 inhibitors leads to osmotic diuresis therefore reducing intravascular volume. [4]

Aim: This meta-analysis aims to evaluate the risk of UTIs, genital mycotic infections (GMIs), volume depletion related adverse events and osmotic-diuresis related adverse events associated with canagliflozin, in comparison with placebo, in patients with T2-DM.

Methods: The electronic databases Medline, Cochrane Library and clinicaltrials.gov were searched for phase 2 and 3 randomized placebo controlled trials evaluating canagliflozin in the treatment of T2-DM. A Mantel-Haenszel odds ratio (OR) with 95 % CI was calculated for all the adverse events of interest, using the random-effects model. The I^2 statistic test was used to assess for heterogeneity between studies. A meta-regression was conducted in order to examine the incidence of GMI and UTIs according to canagliflozin different dose regimens.

Results: Eleven clinical trials were included in this meta-analysis. Canagliflozin was found to be associated with an increased risk of GMIs (OR 5.21; 95 % CI 3.76–7.22, $p < 0.001$; $I^2 = 0$ %). The incidence of GMIs is increased in women (OR female *vs.* male 2.46; 95 % CI 1.80–3.78, $p < 0.001$; $I^2 = 30.7$ %). Treatment with canagliflozin did not increase the incidence of UTIs (OR 1.11; 95 % CI 0.98–1.38, $p = 0.370$; $I^2 = 0$ %). The risk for osmotic-diuresis related adverse events is increased in patients receiving canagliflozin (OR 3.46; 95 % CI 2.23–5.38, $p < 0.001$; $I^2 = 5.5$ %). Incidence of volume depletion related adverse events did not differ between canagliflozin and comparators (OR 1.74; 95 % CI 0.98–3.08, $p = 0.058$; $I^2 = 0$ %). According to meta-regression results, different doses of canagliflozin have similar effects in the incidence of GMIs and UTIs.

Conclusion: Canagliflozin is associated with an increased risk of volume depletion related adverse events and GMIs, the latter being more frequent in women than men. Long-term studies should be conducted to evaluate the recurrence of these adverse events, in order to better elucidate canagliflozin' benefit-risk ratio.

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Abstract Code: P-060

Drug-Safety Alerts Issued by Regulatory Authorities: Usefulness of Meta-Analysis in Predicting Earlier Risks

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Introduction: Meta-analysis is commonly used to assess efficacy.[1,2] Although not frequently conducted to assess safety issues, cumulative meta-analysis has demonstrated that appropriate and timely decisions could have been taken concerning cardiovascular events associated with rofecoxib.[3]

Aim: To evaluate how risk estimates generated from cumulative meta-analysis performs over time for drugs having their benefit/risk ratio re-evaluated due to safety issues and, additionally, compare risk estimates with regulatory authorities' conclusions.

Methods: Drug-safety alerts issued for the first time between 01/2010 and 12/2012 and which have been supported by longitudinal, comparative studies (both clinical trials and/or observationals studies) were searched in the websites of four major regulatory authorities (EMA, FDA, Health Canada and Australian TGA).[4] Data from studies was included according to the year they first became available—i.e., the earliest of: online publication date or the correspondent journal issue publication date. Random-effects model was used to pool ORs over time and their respective 95 % CI. The influence of studies' publication date over the primary outcomes' risk considered in each safety alert was assessed using meta-regression.

Results: Seventeen alerts issued on nine different safety issues were included in this study. In 2008, proton pump inhibitors (PPIs) were associated with an increased risk for bone fractures (OR 1.25, 95 % CI 1.00–1.55, $P = 0.049$; $I^2 = 83.9$ %); FDA included labelling warnings in 2012. An increased risk for *Clostridium difficile*-associated diarrhea was pooled for PPIs in 2004 (OR 1.89, 1.19–3.02, $P = 0.007$; $I^2 = 54.4$ %); FDA included labelling warnings in 2012. PPIs were associated with pneumonia in 2009 (OR 1.40, 1.06–1.85, $P = 0.017$; $I^2 = 97.4$ %); in 2012 US FDA concluded that B/R ratio should remain positive. Statins were associated with an increased risk for increased blood sugar (OR 1.07, 1.01–1.15, $P = 0.033$; $I^2 = 0$ %) in 2008. EMA included labelling warnings in 2012. The remaining cumulative meta-analyses have not estimated increased risks earlier than regulatory decisions. According to meta-regression results, most of the risk estimates were stable over time. The exception was the risk estimate for statins and increased blood sugar, which progressively increased.

Conclusion: This study demonstrates that meta-analysis may help predicting iatrogenic risks. However, between-studies heterogeneity can

considerably affect the estimated results and, therefore, this technique should not replace further assessments during benefit/risk ratio reevaluations.

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Abstract Code: P-061

Drug Safety Signals Generation Using Disproportionality Analysis of Spontaneous Reporting Databases—A Systematic Review

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Introduction: Spontaneous reports are an important tool in pharmacovigilance. Detection of safety signals can be made more efficient by the use of quantitative methods or data mining.[1,2] The most frequently used is disproportionality analysis. These methods measure disproportionality and quantify unexpectedness, meaning that the observed number of reports for a specific drug–adverse event combination is higher than expected from the total database reports.[2]

Aim: This study aimed to perform a systematic review of studies using disproportionality measures applied to spontaneous reports databases to detect safety signals and to evaluate their impact in further regulatory actions.

Methods: MEDLINE database and Cochrane Central Register for Controlled Trials (CENTRAL) were searched, from 2003 to 2013, in order to identify studies reporting the application of disproportionality measures to detect a safety signal. All selected publications were assessed to identify the generation of a signal of disproportionate reporting (SDR) and further regulatory actions taken.

Results: Fifty-seven studies were included, mostly reporting on a 'drug-adverse event' pair. National and regional databases were identified. The disproportionality measures applied include frequentist and Bayesian methods and some studies used more than one method. Almost 90 % of the selected studies identified a SDR. Only for two cases regulatory actions were undertaken.

Conclusions: The application of disproportionality measures to spontaneous reporting databases was found to be useful in the generation of research hypotheses, while its direct contribution for regulatory actions was found to be modest.

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Abstract Code: P-062

Safety Monitoring of Ophthalmic Biologics: A Systematic Review of Pre- and Post-Marketing Safety Data

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Introduction: Recently, three biologics were approved for the treatment of ocular diseases. The safety of ophthalmic biologics has been studied in randomized controlled trials (RCTs); however, the predictability of preclinical to clinical data is limited for biologics compared to small molecules due to biologics' specific characteristics.[1,2]

Aim: The present study characterizes the safety profile of ophthalmic biologics, in both pre- and post-marketing settings.

Methods: The European Medicines Agency website was searched to identify biologics with approved ophthalmologic therapeutic indications. A systematic search was performed using MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the International Clinical Trials Registry Platform up to December 2013. Pre-marketing, phase III RCTs, post-marketing clinical trials, observational longitudinal studies and case reports involving adverse events (AEs) were included. Methodological quality was assessed by the Downs & Black checklist. All European spontaneous reports of AEs included in the Eudravigilance up to December 2013 were also considered. AEs were classified as ocular (related and non-related to the injection procedure) and non-ocular (related or non-related to VEGF inhibition). Incidences of all reported AEs were estimated.

Results: Pegaptanib, ranibizumab and aflibercept were identified as ophthalmic biologics. Fourteen pre-marketing RCTs, seven post-marketing clinical trials, 31 observational studies, along with 31 case reports and 7720 spontaneous reports were identified and included in this study. In both pre- and post-marketing settings, ocular AEs were more frequent than non-ocular AEs. Pre-marketing safety data provided the most common AEs. Post-marketing studies suggest an increased number of events such as retinal pigmented epithelium tears (0.6–24 %), thromboembolic events (0.8–5 %) and mortality (2.8–4 %).

Conclusions: This study highlights the need to properly evaluate the risk for rare, serious and long-term AEs, such as thromboembolic events, since they can imbalance the benefit-risk ratio of biologics in ophthalmology.

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Abstract Code: P-063

Quantitative Methods for Detecting Signals of Drug–Drug Interactions—A Comparison of Two Approaches

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Aim and Hypothesis: Detection of potential signals in spontaneous ADR databases relies heavily on automated quantitative screening using statistical methods. These methods show whether the frequency of reporting of an ADR with a given drug (drug-ADR pair) is higher than the background frequency of reporting of the same ADR in the whole database for all other drugs (methods of disproportionality). There have been numerous comparisons of the various methods of disproportionality used in spontaneous reporting systems for the detection of signals. [1–5] However, a systematic comparison of non-Bayesian (i.e. reporting odds ratio) and Bayesian methods (i.e. the Omega measure, as proposed by Noren et al.[6] to detect signals arising from ADRs resulting from drug–drug interactions, i.e. a drug–drug-ADR triplet) on a large number of drug–drug-ADR triplets has not been investigated. The aim of this study is to compare the reporting odds ratio and the Omega measure on a set of known drug–drug interactions using data from the European union adverse drug reactions database (Eudravigilance).
Methods: To make any comparison of the above approaches, a reference dataset of known drug–drug-ADR triplets must be made. Known triplets will be extracted from the Stockley's Drug Interactions Online database. Formulae used in previous studies for reporting odds-ratio and the Omega measure will be applied to the same dataset in Eudravigilance. As a final step in the process, the level of concordance between reporting odds ratio and Omega measure with regard to the reference set (known and potential triplets) will be expressed in terms of sensitivity, specificity and positive or negative predictive value. Finally, the results would be stratified by the number of reports in Eudravigilance when the number of reports in Eudravigilance is: $n \geq 2$; $n \geq 3$; $n \geq 4$; $n \geq 6$.
Conclusions and Implications: Statistical analyses have proven to be a valuable tool in detecting the signals of disproportionate numbers of drug-ADR pairs reporting in these systems. There is, however, no gold standard in terms of types of statistical analyses used. This study should show what the level of concordance is between the reporting odds ratios and Omega measure to the detection of drug–drug interactions, specifically for the Eudravigilance database. The results of this study should complement earlier studies done in the field of the detection of drug–drug interaction signals and aid in deciding which method should be used to detect drug–drug interactions in the spontaneous ADR databases.

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Abstract Code: P-064

Signal Detection for Thai Traditional Medicine

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Introduction: The safety information of Thai Traditional Medicine (TTM) including herbal medicine was lacking in the pre-marketing period, however a regulatory agency is necessary for timely estimate potential risk. Early detection of unexpected numbers of adverse drug reactions (ADRs) suspected with TTM abnormally reported from the whole database needs quantification. Disproportionality analysis was performed for signal detection by using reporting odds ratio (ROR). The impact of having medicine as exposures in each reported ADR measured by using reported population attributable risks (RPAR).
Aim: To assess the association between TTM and serious ADRs.
Methods: Data was retrieved from the ADR surveillance database, Thai-Food and Drug Administration from 2002–2013. Reports contained at a minimum information on reporters, patient characteristics, ADRs and suspected drug. Reports with causality assessment level 'unlikely' were excluded. RORs of TTM and serious ADRs with a number of reports > 3 and upper limit of 95 %CI > 1 were considered as potential signal.[1] Potential risk factors for serious ADRs were age group, gender, history of allergy, underlying disease and number of drugs used, were included for adjustment in a logistic regression. RPARs were computed from adjusted RORs[2]. All analyses were done using Epicalc package on R language and environment version 3.0.2.
Results: Five hundred and two ADRs reported associated with TTM notified from 290 health facilities were eligible for analysis. There were nine TTM-ADR pairs out of 4208 drug-ADR pairs of potential signal. Three TTM-Serious ADR pairs were examined. The TTMs with serious ADRs had statistically significant RORs (crude), namely *Andrographis paniculata* and anaphylactic shock (ROR 2.32; 95 %CI 1.03, 5.21); green

traditional medicine and Stevens-Johnson syndrome (ROR 13.04; 95 %CI 5.4,31.51) and *Derris scandens* Benth and angioedema (ROR 2.71; 95 %CI 1.05, 6.95). Their RPARs ranged from 0.05–0.16 %.

Table I presents number of reports, adjusted RORs and RPARs for each serious ADR suspected to be associated with the TTM. Conventional medicine with a high number of reports and high RORs for those serious ADRs are highlighted in the table.

Conclusions: Although the number of ADR reports associated with TTM was small, there was no apparent difference in proportion of serious ADRs between TTM and conventional medicines. Three TTMs were significantly associated with serious ADR. ThereforeTTM needs more intensive surveillance.

Table I Number of serious TTM ADR reports and adjusted ROR and RPAR

ADR	Drug	No. of reports	ROR_{adjust} (95 %CI)	RPAR (%)
Anaphylactic shock	*Andrographis paniculata*	6	2.68 (1.19, 6.04)	0.05
	Diclofenac*	722	1.28 (1.15, 1.41)	2.28
	Penicillin G†	11	15.63 (8.14, 30.04)	0.16
Steven Johnson syndrome	Green traditional medicine	6	19.47 (7.82, 48.49)	0.05
	Cotrimoxazone*	1,622	4.53 (4.27, 4.8)	11.97
	Carbamazepine†	862	22.36 (20.54, 24.35)	7.80
Angioedema	*Derris scandens* Benth	5	2.68 (0.93,7. 74)	0.01
	Diclofenac*	2461	2.89 (2.75, 3.03)	6.15
	Dorzolamaide and timolol†	4	8.25 (2.04, 33.36)	0.01

* Drug with highest number of report; † Drug with high ROR

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Abstract Code: P-065

Deliberate Self-Poisoning with Drugs in Mali: An 11-Year Retrospective Study

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Introduction: Deliberate self-poisoning is a major hidden public health problem around the world and the most common method of attempted suicide.

Aim: The present study aims to determine the main characteristics of drug self-poisoning in Mali.

Methods: This is a descriptive retrospective analysis of intentional poisoning cases, recorded between 2000 and 2010, in the medical records and the consultation register at 15 hospitals in Mali.

Results: There were 654 drug self-poisoning cases diagnosed in Mali, which was 75 % of all intentional poisoning cases reported during the study period. Of these, 85.3 % of the patients were females and 79.2 % were unmarried. Most victims were in their late teens or early twenties. The average age of victims was 21.9 ± 7.4 years. Suicide attempts and self-induced abortion were the most common forms of self-poisoning (59.3 % and 38 % of cases, respectively). The most commonly used drug for self-poisoning was chloroquine (67 %). The poisoning effects vary depending on the type of drug consumed, the dose taken and the delay before treatment. Among the 648 cases for whom the outcome was known, 45 (6.9 %) of the patients died. For other cases, the outcome was favorable with or without sequelae.

Conclusions: Drug self-poisoning remains a major public health problem in Mali. The number of victims is probably underestimated because of undiagnosed and unreported cases.

Abstract Code: P-066

Key Features of Medication Error Reporting in VigiBase

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Introduction: Medication error (ME) reports are collected by several national pharmacovigilance centres and shared within the WHO programme. National pharmacovigilance centres have identified preventable risks related to ME by evaluating spontaneous reports.1–3 So far, there has been no overall analysis of these reports on an international level.

Aim: Describe the reporting of medication errors in the WHO programme for international drug monitoring and identify its key features.

Methods: The analysis was performed in the WHO global ICSR database, VigiBase® as of June 2013. Reports with terms subordinated to the MedDRA® high level group term 'Medication errors' (excluding preferred terms 'Intentional overdose' and 'Overdose') were retrieved. Descriptive statistics for country of origin, patient demographics, reporter qualification, co-reported drugs and co-reported adverse events were obtained for the set of medication error reports. To identify their key features, we utilized vigiPoint, a method for rapid, open-ended pattern discovery based on shrinkage odds ratios (OR). [4] Specifically, we contrasted ME reports with all other reports in VigiBase and identified key features as covariate values or ranges for which the 99 %CI of the shrunk $\log_2$ OR with ME reports was above 0.5. Results are presented with MedDRA high level terms and with the WHO Anatomical Therapeutic Chemical classification (level 3).

Results: 164,000 ME reports were characterised and compared with 7,833,000 reports in VigiBase. ME reporting has increased over time and was significantly elevated in 2012 and 2013. Sixty-five countries have reported ME, of which the US was the only one with a greater than

expected contribution (89 % of ME reports vs. 50 % for VigiBase overall). 53 % of ME reports were sent in by consumers vs. 17 % of VigiBase reports on other events. Other key features were a higher than expected number of reports from pharmacists (12 % vs. 5 %) and lawyers (2.9 % vs. 1.5 %), as well as for patients aged 2–11 years (10 % vs. 6 %). Within this age group accidental overdose was a commonly reported term. Top reported highlighted groups of drugs were: opioids, antipsychotics and drugs for peptic ulcer and gastro-oesophageal reflux; and groups of events were: maladministrations, medication errors NEC and overdoses.

Conclusion: In line with previous studies, [1] the greater than expected proportion of reports sent by consumers and non-health professionals suggests that spontaneous reports could be particularly important in the collection and detection of inappropriate medication use outside hospital care.

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Abstract Code: P-067

Potential Risks from Counterfeit Herbal Products Intended for Slimming and Weight Loss

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Introduction: Counterfeit medicines are a global threat and can seriously affect patients' health. [1,2,3] Weight-loss herbal products could be counterfeit not meeting quality standards. Cultural practices consider herbal products safe and promote self-care without medical consultation.
Objective: This study assessed the quality and safety of weight-loss herbal products and evaluated undeclared active ingredients.
Methods: Samples were collected via inspection or referred by patients from April 2005 till March 2014. Detection of ingredients in herbal products was performed by high performance thin layer chromatography and ultraviolet absorption scanning using CAMAG TLC scanner in Drug Quality Control Laboratory, UAE.The labels and health claims were evaluated and adverse drug reactions (ADRs) were monitored via voluntary reporting.
Results: 73/78 (93.6 %) herbal products were confirmed to be counterfeit containing either single or combined active ingredients. Sibutramine and phenolphthalein were the most common active ingredients. (Table I). 10/73 products (13.7 %) contained neither label nor trade name while 63/73 (86.3 %) products were labelled with 'slimming', 'burning fat' or ordinary labels. 32/73 (43.8 %) showed details of manufacturer name, batch number and country of origin, while 33/73 (45.2 %) didn't contain batch number, 28 (38.5 %) didn't contain manufacturer name details and 24 (32.9 %) didn't contain country of origin. No manufacture details, batch numbers or country of origin appeared on 14 (19.2 %) of products. ADRs were evaluated from 5 patients. Three patients (60 %) were taking herbal products containing sibutramine, of which two patients (40 %) reported increased heart rate and high blood pressure while one patient (20 %) reported constipation and headache. Two patients (40 %) taking herbs containing phenolphthalein suffered abdominal pain and diarrhoea. The low rate of ADR reporting is due to the fact that patients are reluctant to disclose ADRs related to weight loss and the misconception that herbal preparations are safe.

Table I Percentage of single and combined active ingredients in weight-loss herbal products

Single products	Percentage 50/73 (68.5 %)	Combined products	Percentage 23/73 (31.5 %)
Sibutramine	29/73 (39.7 %)	Sibutramine, phenolphthalein	16/73 (22 %)
Anthraquinone	7/73 (9.6 %)	Caffeine, theophylline	1/73 (1.4 %)
Caffeine	4/73 (5.5 %)	Caffeine, chromium	1/73 (1.4 %)
Phenolphthalein	4/73 (5.5 %)	Phenolphthalein, anthraquinone	1/73 (1.4 %)
Chromium	4/73 (5.5 %)	Sibutramine, fluoxetine	2/73 (2.7 %)
Fuoxetine	1/73 (1.4 %)	Sibutramine, anthraquinones, theophylline	1/73 (1.4 %)
Hydrochlorothiazide	1/73 (1.4 %)	Sibutramine, phenolphthalein, anthrquinone	1/73 (1.4 %)

Discussion: Many counterfeit medicines don't meet quality standards and don't declare the composition and quantities [4]. Many herbal product labels do not mention active ingredients, manufacturer's details or country of origin [5]. They might contain ingredients such as sibutramine and phenolphthalein or laxatives such as anthrquinone and hydrochlorothiazide or antidepressants such as fluoxetine [2,3]. Serious events such gastrointestinal discomfort or cardiovascular effects could be related to adulteration of herbal products [2,4,5,6].
Conclusion: Adulteration of herbal supplements marketed as natural weight losing is common and purchasing unregistered products from unapproved sources poses risks to patients [4,5,6]. Effective pharmacovigilance systems can help in alerting healthcare professionals and the public to this threat [2,3,5].

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Abstract Code: P-068

Knowledge, Attitude and Practice (KAP) Analysis of Pharmacovigilance (PV) Among Jordanian Healthcare Professionals (HCPs)

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Introduction: Since pharmacovigilance (PV) is highly dependent on reporting of adverse drug reactions (ADRs), a lack of reporting presents an obstacle. In reality, under-reporting in PV is a very common phenomenon worldwide. Despite the presence of PV centers in some countries, the rate of reporting serious reactions may not be more than 10 %. As the extent of PV KAP in Jordan is unknown, this study was designed to assess and measure the extent of Knowledge, Attitude, and Practice (KAP) towards PV among Jordanian Healthcare Professionals (HCPs) and explore some of the reasons behind under-reporting.
Methods: The study was cross-sectional. It included HCPs (physicians, nurses, pharmacists) from generalized and large hospitals in Jordan with number of beds $\geq$200. Hospitals were randomly selected from three different sectors; university, private and governmental. The minimum sample size required was 384 HCPs, but the actual number selected was 600 HCPs to account for potential non-responders.
Per each study site, 200 HCPs were randomly selected. Sampling technique was stratified multistage random sampling.
Results: The response rate in the study was 64 % (382 out of 600 distributed questionnaires). The mean age (standard deviation) was 29($\pm$5) years. The majority of subjects (74 %) were between 21 and 30 years. Subjects were equally distributed in terms of sex. About 70 % of subjects had 1–5 years of experience. Most of the HCPs were nurses (69 %), 24 % were physicians and the lowest percentage were pharmacists (7 %). The results showed that the majority of responders have a "very poor" to "fair knowledge" score. About half have a "good" to "very good" attitude score toward PV, and about 70 % of responders have a "very poor" to "fair" practice score.
Conclusion: The overall knowledge, attitude and practice (KAP) scores were low among Jordanian healthcare professionals (HCPs). The findings showed that the majority of HCPs have "very poor" to "fair" knowledge scores, specifically relating to awareness of local reporting timelines and the adverse drug reaction (ADR) reporting system (unawareness of the availability of the yellow card for ADR reporting). This suggests that the awareness campaign of Jordan Food and Drug administration (JFDA) may have been not sufficient and did not cover all health sectors.

Abstract Code: P-069

Drug-Induced Eosinophilic Pneumonia and NSAIDs

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Introduction: The majority of adverse drug reactions (ADRs) induced by nonsteroidal anti-inflammatory drugs (NSAIDs) are well known, such as bleeding ulcers or renal failure. But there are some other side effects with potential serious aftermaths such as eosinophilic pneumonia.
Methods: This study used all spontaneous ADRs registered into the French pharmacovigilance database and reviewed the literature about eosinophilic pneumonia induced by NSAIDs.
Results: Four reports of eosinophilic pneumonia with NSAIDs were collected in the French pharmacovigilance database. They concerned three men and a woman. The mean age was 48.75 years (between 24 and 68). In two cases, the NSAID was the only suspected drug, and one had a positive rechallenge. All the patients needed hospitalization and recovered in a few days. The main symptoms were cough, dyspnea and fever. In three cases, the NSAID was stopped and the patients recovered. In the fourth case, a corticosteroid therapy was started, and the patient recovered.
Twenty cases were described in the literature. In these, the eosinophilic pneumonia concerned women and men equally. The mean age was 50 years. Onset symptoms of eosinophilic pneumonia were cough, dyspnea, fever, malaise, weakness, headache, chills, myalgia and sometimes crackles or rash. A chest x-ray and scan always showed typical interstitial ground glass opacities. Bronchoalveolar lavage usually showed elevated cell counts, especially eosiniphils. The commonest suspected drugs were naproxen and ibuprofen. Naproxen is the most reported and is the only one with eosinophilic pneumonia clearly mentioned in the SPC. In the majority of cases, patients recovered when the treatment was stopped. In some cases, corticosteroid therapy was added.
Conclusion: NSAIDs-induced eosinophilic pneumonia is a common cause of interstitial pneumonitis. However, the approach to diagnosis is not well defined, and there is no recommendation for the treatment of the patient. The prognosis seems to be good after stopping treatment but the symptoms are invalidating. Prescribers should be informed and aware of this possible ADR. Recommendations should be made about diagnosis and treatment.

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Abstract Code: P-070

Denosumab: Comparative Safety of Two Trade Names

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Introduction: Since 2010, denosumab, under two trade names, has been used to treat postmenopausal women at increased risk of fractures, 60 mg once every 6 months and in the treatment of skeletal-related event prevention in adults with bone metastasis from solid tumors, 120 mg dose by subcutaneous injection every 4 weeks. Denosumab is a new class of osteoporosis treatment called a human monoclonal antibody that prevents RANKL–RANK interaction, and inhibits osteoclast function. The antibody is produced in genetically engineered mammalian cells.
Aim: To compare the safety profile of the two denosumab marketed presentations.
Methods: Spontaneous French notifications of adverse drugs reactions (ADRs) were registered into the French Pharmacovigilance Database (FPDB). During the study period (year 2013), spontaneous reports from the FPDB were collected. ADRs were considered according to the Medical Dictionary for Regulatory Activitives (MedDRA®) primary System Organ Class (SOC). Reimbursement estimations (year 2013) were extracted from Medic'AM, the French healthcare reimbursement website.
Results: During the study period, 23 notifications were reported (19 in the oncologic indication) with 39 adverse events (mean age 66.8 years [p = 0.95; CI: 56.9, 76.6]). In 2013, 3.315 units of the 60 mg denosumab presentation were reimbursed, corresponding to one notification for 828 units. Ten ADRs were collected; all of them concerned women, including one serious adverse event. The three major SOCs were "Nervous system disorders", "Skin and subcutaneous tissues disorders" and "Gastrointestinal disorders". For the second presentation, 68.663 units were reimbursed in 2013, corresponding to one notification for 3613 units. 29 ADRs (22 serious) were notified (16 women). The three major SOCs were "Nervous system disorders", "Metabolism and nutrition disorders", and "General disorders and administration site conditions".
Conclusion: Nervous system disorders were notified in oncologic indication, but not mentioned in the SmPC. However, the safety profile of the product corresponds to the SmPC. In our study, adverse events were more frequently reported with the low dose of denosumab. These results confirm the under-reporting in oncology.

Abstract Code: P-071

Method for the Minimization of Competition Bias in Safety Signal Detection

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Introduction: Performance of signal detection in spontaneous reporting databases can be affected by competition bias, which occurs when an adverse drug reaction (ADR) is so widely reported in association with a drug or a group of drugs that it reduces the probability of the detection of signals concerning other drugs [1,2].
Aim: To develop and to test the performance of an automated method for the correction of competition bias.
Methods: Reports recorded in the French spontaneous reporting database (FSRD) between 2000 and 2005 were selected. Five ADRs were considered: myocardial infarction, acute pancreatitis, aplastic anaemia, seizure, gastrointestinal bleeding. Cases were identified using the corresponding standardised MedDRA queries (broad version). Potential competition effects were investigated using a "Competition Index", defined as the proportion of reports for an ADR mentioning a given drug class. Signal of disproportionate reporting (SDR) detection was performed using Proportional Reporting Ratio (PRR) in two datasets: (i) complete database, (ii) datasets excluding reports related to drug or drug classes, defined according to the Anatomical Therapeutic Chemical (ATC) classification levels 2–5, reaching a given value of Competition Index for an ADR (5–20 %). SDRs detected only in the latter datasets were considered as unmasked; they were classified as "known" if the ADR concerned was mentioned in the drug summary of product characteristics, and "unknown" otherwise. A reference dataset including all unmasked signals was used to calculate sensitivity (Se) and specificity (Sp) for unmasking of each ATC level/Competition Index threshold combination. Competition Index unmasking performance was then compared to those of Masking Ratio (MR)[3] and the Masking Factor (MF) [4].
Results: Among the 82,885 reports recorded in the FSRD, 10,200 were related to the ADRs of interest, for which initial signal detection identified 264 SDRs. The combinations associated with the best unmasking performance were ATC level 3 with Competition Index thresholds of 11–13 %. The ATC level 3/12 % Competition Index threshold combination unmasked 94 SDRs and had a Se of 29 % and a Sp of 75 % for unmasking. In the same setting, MR unmasked 6 SDRs with Se 2 % and Sp 99 %, and MF 4 SDRs with Se 2 % and Sp 100 %.
Conclusion: In this study setting, the Competition Index performed better than other unmasking techniques. Further studies should be performed to determine to the performance of the Competition Index in automated signal detection.

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Abstract Code: P-072

Warfarin Pharmacogenetics—Ethnicity Considerations

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Introduction: Some individuals show an increased susceptibility to certain adverse drug reactions (ADRs) because of genetic polymorphisms that alter their response to drugs. The evaluation of pharmacovigilance-related

issues associated with pharmacogenetics, and the translation of the results of these evaluations to appropriate recommendations in the labelling has the potential to reduce drug-related morbidity [1]. The anticoagulant warfarin is an example of the clinical use of pharmacogenomics to improve dosing. Genetic variants in the warfarin target, the vitamin K epoxide reductase (VKORC1) enzyme as well as the warfarin-metabolizing enzyme, cytochrome P4502C9 (CYP2C9), influence the variation in patient response. The frequencies of the CYP2C9 and VKORC1 variant alleles differ between racial groups [2–6].

Aim: The aim of this review was to determine the frequencies of CYP2C9 and VKORC1 variants in three racial groups, Black, Asian and Caucasian, and to discuss the association between these variants and warfarin response.

Methods: A Medline search was conducted and reference lists of review articles and publications reviewed. CYP2C9 (alleles *2 and *3) and VKORCI (-1639G/A) were selected as target genes as polymorphisms on these genes have shown a consistently significant influence on warfarin response. VKORC1 −1639G/A polymorphisms were categorized based on the presence of the −1639A allele (AA and AG versus GG), the "A allele carrier" group.

Results: The frequency of the genetic polymorphisms according to ethnicity is reported in Table I. CYP2C9 polymorphisms are most frequent in Caucasians and variants are absent or rare in Blacks and Asians. CYP2C9 variants are associated with warfarin sensitivity, decreased warfarin dose and increased bleeding complications. The frequency of the AA genotype on the −1639G>A variant allele of the VKORC1 gene predominates in Asians and is associated with warfarin resistance.

Conclusions: The case of warfarin provides an example of how ethnic diversity can affect response to therapy. Genotyping individuals prior to initiating therapy with drugs whose response is known to be affected by pharmacogenetics could minimize the risk of ADRs and improve drug safety.

Table I Frequencies of the CYP2C9 and VKORCI polymorphism by ethnicity [2–6]

Genotype	Caucasian (%)	Black (%)	Asian (%)
VKORCI—1639 G/A AA	10.8	0	81
VKORCI—1639 G/A AG	52.5	20.8	18.1
VKORCI—1639 G/A GG	36.8	79.3	1
CYP2C9—*1/*1 (wild-type)	65.2	90.3	95.5
CYP2C9—*1/*2	20.5	2.2	0
CYP2C9—*2/*2	1.4	0	0
CYP2C9—*2/*3	1.4	0	0
CYP2C9—*1/*3	13.4	3.1	4.9
CYP2C9—*3/*3	1.6	–	0

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Abstract Code: P-073

Safety Profile of Propofol, Midazolam, Diazepam and Lorazepam using the Korean Adverse Event Reporting System (KAERS) Database

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Introduction: Propofol is known to be safe but is an addictive substance, and cases related to the misuse or overuse of propofol have been a serious problem in Korea as well as in many other countries. [1–3]

Aim: To assess the safety profiles of propofol and three other addictive anesthetics using the database from the Korean Adverse Event Reporting System (KAERS).

Methods: The domestic supply data of four anesthetics from 1 January 2008 to 31 December 2012 were retrieved, and the total adverse drug reactions (ADRs) submitted to KAERS were retrieved during the same period. ADR proportions were also calculated using supply data (defined daily dose/1,000 inhabitants/day, DID) for the denominator. The patient's characteristics were compared among the four drugs statistically, and the types of ADRs were analyzed in terms of System Organ Classes (SOC) and Preferred Terms (PT) of World Health Organization Adverse Reaction Terminology (WHO-ART).

Results: The consumption and ADR reports showed an increase during the study period, particularly in the cases of propofol and midazolam in Korea. In the total ADR reports (3,375), the patient's characteristics showed statistically significant differences among the four drugs in terms of gender, age, and the number of concurrent medications. Lorazepam showed the highest overall and serious ADR proportions (220.81 reports/DID and 58.47 reports/DID, respectively); however, with respect to death proportion, propofol was the first (19.21 reports/DID). As a result of the SOC and PT analysis, gastrointestinal system disorders were frequent ADRs of propofol, midazolam, and diazepam, whereas psychiatric disorders were frequently observed in patients administered lorazepam. However, PTs related to drug addiction like drug abuse or drug dependence were mainly observed in the propofol group relative to the other anesthetic groups.

Conclusion: Four anesthetics were different with regard to the recent use status and proportion or the type of ADRs. The use of propofol increased rapidly compared with the other anesthetics, and this anesthetic showed the highest ADR proportions in death and drug addiction cases among the four anesthetics.

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Abstract Code: P-074

Relationship between Structural Alerts in Drugs and Reported Idiosyncratic Hepatotoxicity in the WHO-Database

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Introduction: Idiosyncratic drug reactions represent one of the major causes of drug withdrawal from the market. According to the reactive metabolite (RM) concept this may be due to the metabolic activation of chemical moieties in the parent drug (the so-called structural alerts or toxicophores) into reactive metabolites. Avoidance of structural alerts in drug design may lead to less idiosyncratic drug reactions and improve drug safety. In the less optimal situation where the structural alert cannot be replaced, idiosyncratic adverse drug reactions may be somehow predictable. Additionally, drug-induced hepatotoxicity and drug-induced auto-immune disease are more frequently associated with compounds administered at high daily dose: for two compounds possessing the same structural alert, it is frequently the case that the low-dose compound will not cause toxicity whereas a higher dose compound will. The evidence that metabolic activation of structural alerts leads to adverse drug reactions manifested as in vivo toxicity, is up to now circumstantial.
Aim: To study the relationship between the number of known structural alerts in NSAIDs (the bromobenzene ring, the aryl acetic group, and the aniline ring) and idiosyncratic hepatotoxicity.
Methods: We calculated the reporting odds ratios (RORs) for five NSAIDs (bromfenac (W), lumiracoxib (W), diclofenac, ibuprofen and naproxen) associated with the MedDRA preferred terms: hepatic failure, hepatic function abnormal, hepatic necrosis and hepatitis. The strength of the association of these ADRs is compared with the preferred term haemorrhage, an ADR not associated with the forming of RMs.
Results: Based on the reported ADRs in the WHO-database, associations with NSAIDs with structural alerts (SAs) (bromfenac, lumiracoxib, diclofenac) are reported more disproportionately compared to drugs where steric hindrance is introduced to decrease the effect of the SAs (ibuprofen and naproxen). The extent of disproportionate reporting of ADRs related to hepatotoxicity correlate with the number of SAs and the daily doses (DD) of the drugs. The extent of disproportionate reporting for the ADR haemorrhage, which is not associated with the forming of RMs, is not related to the number of SAs or daily dose.
Conclusion: The results of this study are supportive for the reactive metabolite concept and are, so far, one of the first linkages between this concept and in vivo toxicity measured as spontaneously reported ADRs in the WHO-database. However, since information on the precise role of RMs in the reported ADRs is lacking, involvement of other mechanisms leading to hepatotoxicity cannot be excluded.

Abstract Code: P-075

Comparative Study on the Pattern of Erectile Dysfunction Treatment Drug Usage Among Hospital Patients and the General Population

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Introduction: Phosphodiesterase type 5 inhibitors (PDE5Is) have been found to be highly effective and well tolerated, and are available as the first-line therapy for the treatment of erectile dysfunction (ED) [1–3]. Since the patent for Viagra is set to expire in May 2012 in Korea, PDE5I drugs that are commercially available in Korea were significantly expanded. In addition, increased use of cheaper generics and the risk arising from the use of counterfeit drugs are expected.
Aim: To compare the utilization pattern of non-prescription PDE5Is drugs between the general male population and patients who came in to the department of urology for the treatment of ED
Methods: Questionnaire surveys were performed in 1,500 nationally representative general males in May–July 2013 using computer-assisted telephone interview (CATI) and 920 patients who came to the department of urology of 32 medical institutions consisting of 10 university hospitals and 22 clinics in October-December 2014. The questionnaire included experience or not with taking non-prescription PDE5I drugs and to AEs after taking PDE5I drugs
Results: 1,015 (68 %) in the survey of general men and 292 (32 %) in urological patients answered that they have used the non-prescription PDE5I drugs. 1,061 (78.6 %) and 232 (79.5 %) in two groups answered "through friends and colleagues" about the route of obtaining non-prescription PDE5I drugs. 121 (67.4 %) and 167 (57.2 %) answered "to be able to easily obtain" about the reason for obtaining such a route. 1,240 (82.7 %) and 838 (91.1 %) know that prescription PDE5I drugs are safe compared with non-prescription those. However, 7.1 % in general men and 8.5 % in urological patients answered that PDE5I drugs with and without prescription have similar safety. 973 people (65 %) in general men and 485 people (53 percent) in urological patients have experienced the AEs of PDE5I drugs. Hot flushing was most frequent AE symptom in both groups.
Conclusions: Men from the general population have taken non-prescription PDE5I drugs more than twice as much as patients who were admitted to the hospital for the purpose of ED treatment. These data show that general population men are more prone to exposed to counterfeit PDE5I drugs and not aware of the risk in PDE5I drug use than patients admitted to the hospital.
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Abstract Code: P-076

Development and Evaluation of an Algorithm for Named Entity Recognition of Drugs in Global Pharmacovigilance

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Introduction: A unique value of individual case reports of suspected harm from medicines is their ascertainment of information specifically aimed to support causality assessment. Ideally, most of this information will be structured but this is not always so, and some nuances cannot easily be captured by structured data fields. A first step towards unlocking the value of case narratives for large-scale analysis is to develop methods for automatic identification of references to drugs and medical events in free text. A global context requires a global drug reference list, but the fact that many common English words are names of drugs in some part of the world makes it difficult to maintain an acceptable false positive rate.

Aim: To develop and evaluate a named entity recognition algorithm for drugs in global pharmacovigilance.

Methods: Reports with case narratives in English were randomly selected from the WHO global individual case safety reports database VigiBase [1]. 242 reports were used for developing the algorithm, and a separate set of 333 reports was used for evaluation. Two pharmacists identified and annotated references to medication names, as gold standard for algorithm training and evaluation.

A predictive algorithm was developed, combining the WHO Drug Dictionaries for lookup, with logistic regression for word sense disambiguation. For reference, we evaluated the proportion of unique medication names in the narratives included in RxNorm [2] and the WHO Drug Dictionaries, respectively.

Results: The diagnostic performance of our algorithm for annotating drug names, expressed in terms of sensitivity and positive predictive value was 0.91 and 0.92, respectively. In contrast the performance of naïve annotations by the WHO Drug Dictionaries without disambiguation yielded a sensitivity of 0.95 and a positive predictive value of 0.19. 73 % of the unique medication names were available in RxNorm compared to 99 % in the WHO Drug Dictionaries.

Conclusion: Effective drug name entity recognition in a global context requires a global dictionary, which in turn requires sophisticated analytics to maintain acceptable positive predictive value. Our algorithm combines use of the WHO Drug Dictionaries with a predictive algorithm for word disambiguation and achieves high sensitivity and positive predictive value for identification of drug names in free text narratives of individual case safety reports. Further research is needed to explore how it can incorporate fuzzy text matching to handle misspellings and be combined with semantic analysis.

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Abstract Code: P-077

Monitoring Batch-Related Safety of Vaccines

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Background: In the National Vaccination Program (NVP) of the Netherlands, a variety of vaccines is used of which the manufacturing and quality control is based on production batches. Since these vaccines are being used in a large number of children, a real time signal detection procedure is needed to be able to detect this type safety signals and take adequate measures once a potential safety signal arises. Aim of this paper is to study the feasibility of the implementation of batch related analysis in the Netherlands in terms of the number of batches to be analyzed, number of potential signals generated and practical problem encountered.

Methods: When reporting an Adverse Event Following Immunization (AEFI) on a vaccine used in the NVP in the Netherlands, a batch number is asked for on a structured web based reporting form. In a subsequent analysis, reports are grouped in four different categories, i.e. AEFIs related to reactogenicity, possible infections, lack of efficacy and serious AEFIs. The number of reports on these AEFI groups per batch is being compared to all other reports received on vaccines with the same composition and expressed as a reporting unadjusted odds ratio (ROR) with corresponding 95 % confidence interval. Analyses are carried out automatically and are subsequently assessed by a qualified assessor.

Results: Between 1 January 2012 and 1 June, 2014 a total number of 3,126 reports of AEFIs in respect to the NVP were received. The batch number was retrieved in 1,680 (53.7 %) reports of vaccines used in the NVP. Additional analysis of the associations that were statistically significant more frequently reported did not reveal a clinically relevant safety signal so far.

Discussion: Although a batch number is not always available, disproportionality analysis can be used to monitor batch related safety issues. Practical problems encountered were missing or incorrect batch number and the fact that in the NVP two vaccines may be administered concomitantly, hampering a correct attribution of the AEFI to the vaccine. Given the fact that a batch number is initially missing in the majority of cases, a close collaboration with the institutions responsible for the distribution and accounting of vaccines is needed to ensure reliable information about these numbers. Since the number of false potential signals in high, multiplicity adjustment is advisable.

Conclusions: A partially automated processing and analysis of batch related problems enables a real time monitoring for batch related problems for monitoring vaccine safety on a national level.

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Abstract Code: P-078

Traditional Chinese Medicine and Other Phytotherapeutic Preparations Associated with Drug-Induced Liver Injury

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Introduction: Traditional Chinese Medicines (TCM) and phytotherapy play an important role in health care. All TCM products should be approved by CFDA before marketing. All legal drugs in China will be tracked by electronic supervision code by the end of 2015. With the increasing use of TCM and phytotherapy world-wide, CFDA and WHO Uppsala Monitoring Centre (WHO-UMC) have started close collaboration to strengthen the pharmacovigilance of these products. By October 2012, the WHO-UMC database contained over 7.5 million case reports of suspected ADRs, of which over 34,000 concern herbal medicines(HMs)[1].

Aim: To review and summarize (1) current status of Pharmacovigilance of phytotherapy/TCM and suspected drug-induced liver injury (DILI) in China, (2) associated commonly used agents and the preventive measures of concerning TCM/phytotherapy DILI.

Methods: We searched PubMed using the terms *TCM, herbal medicine, Chinese herb/herbs and DILI*. We also reviewed the signals issued in China ADR Bulletin.

Results: (1) China National Center for ADR Monitoring received 1,317,337 ADR/ADE case reports in 2013. Of these reports 17.3 % concerned TCM drugs.[2] It has been reported previously that 20–30 % of DILI case reports are associated with TCM in China [3, 4]. But there are no high-quality epidemiologic data available on the prevalence of DILI in connection with TCM/phytotherapy. (2) We present a list of TCM and phototherapy preparations with potential hepatoxicity. (3) The quality of related literature needs to be improved. Some of the suspected phytotherapeutic preparations reported in association with DILI were not truly TCM medicines but were regarded as such by the reporter. (4) We distinguished three DILI types: cholestatic, hepatocellular and mixed lesions. (5) The absence of appropriate diagnostic criteria and lack of ADR information communication may have led to the low awareness of DILI related to TCM and phytotherapy among global physicians.

Conclusions: In the last two decades, the safety monitoring and risk management of TCM DILI in China have made progress [5]. The evaluation of DILI risk factors associated with phytotherapeutic medicines requires establishment of large database platform for recording and linking of the DILI monitoring data, perfecting the international drug dictionary of phytotherapeutic preparations, scientific research especially in potential genotoxicity study should be involved in the mechanism research, better quality control in manufacturing, standardization of clinical practice,[6], enforcement of voluntary and active surveillance, as well as safety information communication and research cooperation.

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Abstract Code: P-079

Characterization of Safety Alerts Associated with Labeled "Chinese Medicines": Analysis of Healthy Canadians Safety information from 2004–2014

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Introduction: All Natural Health Products (NHPs) in Canada must obtain a product license before manufacturing, marketing and using according to NHPs Regulations issued in 2004. These regulations enforce the safety of NHPs remarkably.

Aim: 1.To review the safety alerts associated with labeled "Chinese Medicine"(CM) released by Health Canada, 2. To analyze the similarities and differences between China and Canada in CM safety and risk evaluation.

Methods: We performed a retrospective search for the safety alerts released by HealthCanada from January 2004 to June 2014 with "Traditional Chinese medicine" (TCM), "CM", "China" and "Chinese".

Results:

1. There are 131 safety alerts labeled with "CM", encompassing 355 products.

2. Product information and signals: (1) Among the 26 identified products approved by CFDA,13 products are related to exceeding local heavy metals standard, 8 products are related to containing aristolochic acids (AA) herbals, 3 products are related to SAE, 2 products counterfeit drugs contained undeclared chemicals. (2) Among 329 products non-registered with CFDA, 11.25 % products are related to AA herbals, 6.38 % products exceeded heavy metals, 5.17 % products associated with bacterial contamination, 254 (77.20 %) products were adulterated with undeclared chemicals. The claimed indications of the 254 adulterated drugs are: 64.96 % products for losing weight, 18.90 % products for sexual enhancement, 7.87 % products for "bone diseases", 4.72 % products for diabetes,1.98 % products for the common cold, 1.57 % products are unclear.

Conclusions:

1. Among 355 products, 7.32 % identified products were registered with CFDA, the involved products include TCMs containing toxic ingredients. CFDA has taken effective measures to control the risk.
2. 92.68 % of the involved products are not certified as TCM; how to identify and fight the counterfeit TCMs is a big challenge for us. It is inappropriate to ascribe safety issues caused by those products to "CM" or "TCM". Drug authorities should strengthen the tracking of serious case reports and communicate with each other to identify the suspected products and manufacturers.
3. TCM and Healthcare food are regulated separately by CFDA. Due to the differences in classification and quality standards among different countries, it is necessary to enhance communication and understanding regarding the safety of TCMs/CMs [1]. The effective ways to enhance global regulatory cooperation are to complete the international drug dictionary of herbal medicines, establish electronic administration tracking system, create appropriate standards for registration and safety control of herbal medicines world-widely.

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Abstract Code: P-080

Two Cases of Interaction between Tacrolimus and Nicardipin in Tunisian Patients

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Background and Objective: Tacrolimus is a calcineurin inhibitor primarily metabolized by CYP3A4 and secondarily by CYP3A5. Several drugs can modify tacrolimus blood levels such as azole antifungals, rifampicin and calcium channel blockers (CCBs). Interaction with nicardipine was reported only in some cases. We report two cases of interaction between tacrolimus and nicardipine.

Results: *Case 1:* A 49-year-old man with a history of malignant arterial hypertension treated by nicardipine underwent a kidney transplantation in 2013. After transplantation, he was treated by tacrolimus, mycophenolate mofetil and corticosteroids. Therapeutic drug monitoring (TDM) of tacrolimus was done regularly showing a mean trough concentration (C_0) of 24.39 ng/mL with some concentrations reaching 52 ng/mL. After the substitution of nicardipine by prazosine, the first tacrolimus C_0 was 3.2 ng/mL.

Case 2: A 51-year-old man, who underwent a kidney transplantation on 22/04/2013, was treated by tacrolimus, mycophenolate mofetil, nicardipine, acebutolol, methyldopa, omeprazole and prednisone. Tacrolimus TDM showed an initial C_0 of 2.5 ng/mL on 05/07/14 for a dose of 0.10 mg/kg that gradually increased to reach 13.5 ng/mL on 17/05/14 for a dose of 0.17 mg/kg. Treatment with nicardipine was stopped on 31/05/14 and tacrolimus dose was not changed. Tacrolimus TDM done on 03/06/14 showed a C_0 at 5.9 ng/mL.

Conclusions: Increasing tacrolimus trough concentrations are due to the inhibition of CYP3A4. Because CYP3A5 is the secondary pathway that becomes important when CYP3A4 is inhibited, very high levels of tacrolimus in the first case suggest the non-expression of CYP3A5. Thus, because of the possible lack of the secondary pathway, therapeutic drug monitoring of tacrolimus is highly recommended at the introduction of CCBs and also on discontinuation.

Abstract Code: P-081

Adverse Drug Effects Induced by Anti-Infective Drugs in Elderly Patients

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Introduction: Anti-infective drugs are widely used. Elderly patients represent a particular cluster also frequently treated by these drugs. Their peculiarities consist of the fact that they have a high rate of polypathology, polypharmacy and alteration of renal or hepatic functions. Certain studies demonstrated that adverse drug effects (ADE) were more frequent and serious in elderly patients. Pharmacovigilance aims to report these ADE, to identify their risk factors and seriousness.

Aim: To identify ADE notified in elderly patients, the prevalence of serious ADE and inducing anti-infective drugs.

Material and Methods: We listed all the cases (134) of ADE induced by anti-infective drugs occurring in elderly patients (age ≥65 years) notified at the Tunisian National Centre of Pharmacovigilance from 1990 to 2006. Imputability was established according to é's method [1] and seriousness according to the OMS criteria.

Results: There were 75 women and 59 men (sex ratio W/M: 1.3). Median age was 70 years (65–92 years). Drugs administered per patient varied between 1 and 10 (average: 2.9) and polypharmacy (≥5 drugs) counted for 25 %. ADE were in 69 % cutaneous, in 13 % anaphylactic, in 9 % digestive, in 4.5 % hematological and diverse in 4.5 %. Cutaneous ADE (92 cases) were: in 33 % maculopapular eruptions, in 15 % pruritic, in 11 % fixed drug eruptions, in 10 % photodermatosis and in 31 % diverse. Anaphylactic ADE were anaphylactic shocks in 5 cases, generalized edema in 4 cases and others in 9 cases. Digestive ADE were hepatic in 10 cases and others in 2 cases. There were 6 cases of hematologic ADE: pancytopenia (2 cases), thrombocytopenia (2 cases) and leucopenia (2 cases). Serious ADE were noted in 37 cases (28 %). Inducing anti-infective drugs were betalactams in 40 %, antifungal and antiparasitic drugs in 16 %, cotrimoxazole in 15 %, antituberculous drugs in 14 %, quinolones in 4 % and others in 11 %. Betalactams were represented by penicillins in 85 % and cephalosporins in 15 %.

Conclusion: Our study is a pharmacovigilance report allowing an overview of ADE and main inducing drugs in order to prevent the occurrence of serious ADE in elderly patients.

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Abstract Code: P-082

Delayed Elimination of Methotrexate and Possible Origins

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Introduction: Methotrexate (MTX) is a folic acid antagonist used in high doses intravenously mainly in the treatment of acute leukemia. Its elimination is renal. Its adverse effects are renal, gastrointestinal, hematological and dermatological. So to prevent potential toxicity, MTX is usually administered following the application of preventive measures.
Aim: To assess the characteristics of patients presenting delayed elimination of MTX and to find out its different origins.
Material and Methods: This was a retrospective study carried out in the Department of Clinical Pharmacology (January–May 2014). Samples were analyzed by an automated fluorescence polarization immunoassay. The inclusion criteria were MTX plasmatic concentration at H72 $>$ 0.1 μmol/mL in patients treated for leukemia receiving high-dose infusion MTX [1]. We collected 35 samples from 19 patients.
Results: Median age was 14 years. Mean dose was 6370 mg/cycle. MTX therapeutic monitoring was performed at least at H72. All the patients had a normal plasmatic creatinine and received a correct hydration. Mean MTX plasmatic concentration at H72 was 0.29 μmol/mL.
Discussion and Conclusion: Delayed MTX elimination is generally due to insufficient hydration and interactions with proton pump inhibitors increasing renal acidity [2]. Gene polymorphism in folate metabolic pathways, in transporter molecules and in some transcription proteins can also induce a delayed MTX elimination.[3] Finally, a medical error can influence this elimination [3]. MTX therapeutic monitoring is recommended till its complete elimination.

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Abstract Code: P-083

Sulfamethoxazole-Trimethoprin and Cyclosporin Interaction in Bone Marrow Allograft Patients

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Introduction: Cyclosporin is a calcineurin inhibitor, used as an immunosuppressant agent in organ transplant recipients, especially in bone marrow allograft patients. Therapeutic drug monitoring is essential because of the narrow therapeutic range, the pharmacokinetic inter- and intra-individual variabilities and the use of several drugs in combination with this drug in this population. The infection remains a common complication in bone marrow allograft patients. Among the antimicrobial agents, sulfamethoxazole-trimethoprin is largely prescribed.
Aim: To assess the influence of sulfamethoxazole-trimethoprin on cyclosporin blood concentration (CBC) in bone marrow allograft patients.
Methods: This was a retrospective study from 1 June to 16 November 2013. We included all the patients who had a bone marrow allograft and were prescribed at the same time cyclosporin and sulfamethoxazole-trimethoprim. Three patients were excluded because of lack of information. Then 63 blood samples from 11 patients were analyzed by an automated fluorescence polarization immunoassay.
Results: Patients' median age was 42 years. Sex ratio M/W was 6/5. Cyclosporin was administered intravenously in 5 and orally in 6 patients. The doses of cyclosporin varied between 40 and 300 mg/day. In 7 patients, there was no variation in CBC or dose. In two patients, CBC varied, decreasing from 11 to 13 % in the second case. In one patient, the dose was increased by 25 % to keep a CBC in the therapeutic range. In one patient, CBC decreased 27 % despite the dose was increased.
Discussion and Conclusion: Sulfamethoxazole-trimethoprim decreases CBC but this interaction remains perplexing. In fact, sulfamethoxazole is a selective inhibitor but not an inducer of cytochrome P450. On the other hand, trimethoprim has been shown to be a substrate but not an inducer of P-gp. Although reported in drug interaction texts, the clinical significance of this interaction remains questionable [1]. Nonetheless, therapeutic monitoring of cyclosporin is recommended when a high dose of sulfamethoxazole-trimethoprim is initiated in order to avoid graft rejection.

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Abstract Code: P-084

Therapeutic Drug Monitoring in Acetaminophen Intoxications

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Introduction: Acetaminophen is classified as an analgesic and antipyretic drug. It is a generally safe drug for use at recommended doses. But intoxication can have serious adverse drug reactions such as liver toxicity which can be fatal. Acetaminophen intoxication is a common means of self-poisonning because of its wide availability and accessibility. Acetaminophen toxicity contributes significantly to intensive care unit

admissions and cost of hospitalization, so acetaminophen therapeutic drug monitoring (TDM) could guide the therapeutic management in these cases.
Aim: To assess the role of TDM in the management of acetaminophen intoxication.
Methods: This was a retrospective study from January 2009 to November 2013. We followed 72 patients seen for acetaminophen intoxication. We collected 83 samples, which were analyzed by an automated fluorescence polarization immunoassay. The toxicity was determined according to the Prescott nomogram.
Results: The patients' median age was 6.75 years and sex ratio (M/W) was 0.6. The mean weight was 28 kg. Among the patients, 27 presented as voluntary intoxication and 45 patients as accidental. Self-poisonings were managed in intensive care units in 96 %. Accidental intoxications were treated in pediatric departments in 84 %.Mean concentration was 40.98 μg/mL. In 17 samples (20.5 %), the concentration was toxic.
Adverse effects were: hepatic (3), digestive (4), hematologic (2), hepatic and hematologic (2) and all three disorders (2).
Conclusion: Although the ingested dose was almost the same in voluntary and accidental intoxications, there were more toxic concentrations in voluntary ones but less adverse effects. This can be explained by an earlier acetaminophen TDM.

Abstract Code: P-085

Phone Communication of Medical Results: Consequences of a Misheard Result

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Background and Objective: Communication is commonly cited as a contributing factor to adverse events causing patient harm [1]. There are numerous ways and reasons that communication failures can occur, such as poor handwriting, transcription errors, lack of verification and lack of integration of information.
We report a case of transcription error due to the verbal communication and reception of results of blood tacrolimus monitoring by telephone.
Case Report: A 44-year-old man was treated with tacrolimus for 7 years for renal transplantation. Regular tacrolimus blood monitoring was performed in our laboratory, test results were transmitted to the prescriber by telephone. The dose of tacrolimus was 2 mg/day from June 2007 to March 2014 with a mean trough concentration (C_0) of 8 ng/mL. In May 2014, a remarkable decrease in tacrolimus blood levels was noted ($C_0 = 1.7$ ng/mL) concomitant with tacrolimus dose reduction (1 mg/day). After contacting the prescriber, we found that the last concentration result was heard as "6.6 ng/mL" and transcripted as "16.6 ng/mL" leading the physician to reduce the tacrolimus dose.
Progressively, the patient developed signs of graft rejection including hypertension, oliguria, elevated creatinine levels up to 838 μmol/mL and an increase in vascular resistance in renal arteries Doppler.
Conclusion: This is an example of how telephone communications between physicians can be misheard and can be life threatening for patients. Certain numbers are more prone to mix-ups. Repeating spoken orders to prescribers and pronouncing each digit of a number (for example "one five" mg instead of "15"mg) can help prevent misinterpretation. It is imperative that error prevention strategies include the read back of a telephone communication. A written transmitted result should also follow the telephone transmission in order to enhance patient safety.
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Abstract Code: P-086

The Value of Patient Reporting in Signal Generation

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Background: Although available literature highlights the usefulness of patient reporting, there is limited information on specific signals generated from spontaneous reports received from patients[1,2]. In 2013, Ghana conducted a mass Measles-Rubella (MR) vaccination exercise, targeting 9 months to 14 year old children, as part of strategies to eliminate measles and Congenital Rubella Syndrome (CRS)[3]. All 11,062,605 vaccinees were placed under vaccinovigilance. Vaccinees and caregivers were encouraged to report Adverse Events Following Immunization (AEFI) directly to the National Pharmacovigilance Centre via phone.
Objective: To identify specific signals generated from spontaneous adverse events reports from patients.
Methods: The routine spontaneous AEFI reporting system in Ghana was used to report AEFI during and 28 days after the campaign covering the period from September 11 to October 18, 2013. Healthcare professionals and vaccinees or their care givers were encouraged to report any AEFI using a standard form or through telephone calls to the National Centre. Potential vaccinees were educated on AEFI reporting through media campaigns and were provided with appropriate phone numbers on their vaccination cards.
Results: A total of 2,677 AEFI reports were received during the 36 day-reporting period. Of these, 1,972 (91.8 %) were received from healthcare professionals and the remaining 705 (8.2 %) originated from vaccinees. The topmost reported AEFI by vaccinees was "double vaccination", (219) at a rate of 19.8 (95 % CI 17.0, 22.3) per 1,000,000 vaccinated compared to 12 reports of "double vaccination" by healthcare professionals at a rate of 1.10 (95 % CI 0.6, 1.9) per 1,000,000 vaccinated. On the contrary, healthcare professionals reported local reactions as the topmost events (785 cases) at a rate of 71.0 (95 % CI 66.1, 76.1) per 1,000,000 vaccinated.
To protect vaccinees from further programmatic errors, The National Pharmacovigilance Centre in collaboration with the Expanded Programme on Immunization sent an alert via telephone and e-mail messages to vaccinators through designated district and regional health officers. This resulted in over 90 % decrease in the incidence of "double vaccination" reports received from patients.
Conclusions: Patient reporting can contribute significantly to signals for events that may not be reported by healthcare professionals, especially, medication and programme-related errors.

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Abstract Code: P-087

Herbal Medicines: Are they Really Safe?

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Background: The World Health Organization (WHO) estimated that 80 % of the world's population uses herbal medicines with the estimate in developing countries as high as 95 % with a global market of approximately US $ 83 billion annually[1]. Interestingly, herbal medicines are not regulated as extensively as conventional medicines and there are limited clinical trials to determine efficacy and safety of traditional herbal medicines[2]. There is a myth amongst users of herbal medicines that herbal medicines are from natural sources and are therefore safe. Users of herbal medicines in most cases do not consider these as "drugs" and in most cases when adverse events results from the use of these products, they are hardly reported.

In Ghana the spontaneous reporting system is designed to receive adverse event reports for both herbal and conventional medicines. However, the reporting rate for herbal medicines is very low: approximately at a ratio of 1:72 compared to conventional medicines.

Objective: To determine the seriousness of suspected adverse events to herbal medicines compared to conventional medicines in the Ghana pharmacovigilance database.

Methods: We conducted a search of the National Adverse Drug Reaction database from 2009 to 2013 to find out the number of suspected adverse event reports received for which herbal medicines are listed as the suspected product compared to conventional medicines.

Results: The National Pharmacovigilance Centre has received total 1,377 spontaneous adverse drug reaction reports from 2009–2013 with an average annual reporting rate of about 12 reports per 1,000,000 population per year. Of these reports 19 (1.4 %) had suspected drug as herbal medicines with the remaining 98.6 % as conventional medicines. Further analysis revealed that 8 (46.1 %) of the 19 suspected herbal adverse drug reactions were classified as serious with 5 (26.3 %) deaths, compared with conventional medicines only 36(2.7 %) were classified as serious.

Conclusion: The analysis of the Ghana's National Adverse Drug Reaction database revealed herbal medicines may have more serious adverse events compared with conventional medicines; this therefore strengthens the need for pharmacovigilance for herbal medicines.

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Abstract Code: P-088

Drug-Induced Stuttering: A Review of the French Pharmacovigilance Database

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Aim: To review the reports of stuttering as an adverse drug reaction (ADR) recorded in the French Pharmacovigilance Database (FPVD).

Method: All the observations with "stuttering" recorded in the FPVD between 1985 until June 2014 were reviewed. We selected all the cases where only one drug was suspected. We collected data on drug involved, characteristics of patients (age, sex and underlying disease) and of ADR (seriousness, delay in occurrence, evolution, imputability and other etiologies).

Results: A total of 51 cases of stuttering were recorded in the FPVD until June 2014. From these cases, 36 in which only one drug was suspected were selected. The male:female sex ratio of the patients included in these reports was 2.4 and the mean age was 40 (min–max: 3–89) years.

The drugs suspected were mainly psychoactives: seven cases with an antiepileptic drug, six cases with a neuroleptic drug (particularly clozapine and olanzapine) and five cases with an antidepressive agent. Two cases involved antihistaminic and antineoplastic agents. Other classes of drug were also involved (one case for each class): TNF-alpha antagonist, vaccine, antibiotic, immunosuppressive agent).

The mean time from introduction of suspected drug to stuttering onset was 80 days (range: 1 day to 3 years). The drug suspected to be involved in the stuttering was withdrawn or the dosage was reduced in 32 cases. Improvement was observed in 29 cases. The drug was maintained in 2 cases but the evolution was not known. In four cases a positive rechallenge was observed (the drugs suspected were rasagiline, olanzapine, carbamazepine and maprotiline). Causality was rated as possible for 22 cases, probable for 9 cases, and likely for 5 cases. Another concomitant cause of stuttering was suspected in 3 cases (psychotic etiology).

Conclusion: Despite the limits of a voluntary reporting database (such as under-reporting), this study confirms that several drugs may induce stuttering in humans. The pathogenesis of developmental, as well as acquired or neurogenic, stuttering is unclear (a part of seizure activity or a variant of movement disorder). Our work also indicates that drug-induced stimulation of central airways elicits stuttering in humans.

Abstract Code: P-089

Characteristics of Patients Exposed to Oral Anticoagulants in a Stroke Hospital-Based Cohort

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Aim: To determine the factors associated with stroke occurring in patients previously treated with oral anticoagulants.

Materials and Methods: This study was conducted in patients admitted to the stroke unit of Lille University and involved in the Biostroke cohort. Patients were included in the 48 h following hemorrhagic or ischemic stroke or transient ischemic attack.

The first step of analysis consisted in a description of the population comparing oral anticoagulant exposure. We used χ^2 test or Fisher's exact test when appropriate and non-parametric Wilcoxon-Mann Whitney test to compare quantitative variables. To determine the factors associated with stroke, we conducted logistic regression where variables with a p-value <0.2 in bivariate analysis were included in the multivariate model. Results were presented with odds ratio (OR) and 95 % confidence interval (95 % CI). Statistical analysis was carried out using SAS 9.1® software (SAS Institute, Cary, North Carolina, USA).

Results: 409 patients with a median age of 70 years (interquartile range, 58–79), 192 women (46.9), were hospitalised for ischemic stroke (n = 370, 90 %) or intracranial haemorrhage (n = 39, 10 %). Among them, 27 (7 %) were treated with oral anticoagulants before stroke. Patients treated with oral anticoagulants presented more with frequently intracranial haemorrhage and less frequently with ischemic stroke than patients not exposed.

Comparison of baseline characteristics between patients treated with oral anticoagulants and patients not treated showed that patients treated were older ($p = 0.0005$), presented more frequently with arterial hypertension ($p = 0.03$), heart failure ($p = 0.02$), and atrial fibrillation ($p < 0.001$) than patients not treated. Stroke was more frequently from cardioembolic origin in patients treated with oral anticoagulants.

Mortality rate, NIHSS, Barthel scale and MMS score at 7 days and 3 months of follow-up after the stroke were comparable in the two groups.

In the second step, the following variables were highly associated with intracranial haemorrhage vs ischemic stroke in the unadjusted model: oral anticoagulation exposure, stroke severity, alcohol consumption, and depression. In the final multivariate model, intracranial haemorrhage (versus ischemic stroke) tended to be independently associated with oral anticoagulation exposure (OR: 2.63; 95 % CI: 0.99–7.11) and was also independently associated with more severe stroke (OR: 0.26; 95 % CI: 0.11–0.6).

Conclusion: These data suggest that stroke occurring in patients previously treated with oral anticoagulants are more frequently haemorrhagic, from cardioembolic origin and concerned older patients, compared to patients not treated.

Abstract Code: P-090

Aortic Dissection during Rivaroxaban Therapy: A Challenging Case

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Aim: To report a case of fatal aortic dissection in a patient treated with rivaroxaban.

Case report: A 65-year-old man (height 191 cm; weight 123 kg) was hospitalized in the Emergency Room for Stanford type A aortic dissection associated with a non-compressive haematic pericardial effusion of 20 mm thickness.

This patient had been treated with rivaroxaban 20 mg once daily for chronic atrial fibrillation and metoprolol (sustained release) 200 mg once daily. He had a history of pulmonary embolism. On admission, haemoglobin was 16.6 g/dL, platelets 155×10^3µg/L, PT 31 % (reference range 70–130 %), international normalized ratio 2.8, aPTT 41 s, and creatinine clearance was 69 mL/min/1.73 m^2. During transfer to the Emergency Room the patient received rehydration therapy and acetylsalicylic acid 250 mg via intravenous injection for suspected myocardial infarction. Rivaroxaban was stopped on admission. On the night following admission, the patient was transferred from a secondary hospital to a cardiac intensive care unit. A surgical intervention was planned but delayed to the next day because rivaroxaban activity was higher than 30 ng/mL (144 ng/mL). Creatinine clearance was 63 mL/min/1.73 m^2. The patient received prothrombin complex concentrate (25 IU/kg, 120 mL). In the morning, he presented with cardiorespiratory arrest on cardiac tamponade with asystolia and received resuscitation measures with oesotracheal intubation, external cardiac massage, and adrenalin injection. A pericardial effusion draining was attempted but was unsuccessful and the patient died.

Discussion: In this case of pericardial effusion in an aortic dissection context, management was complex and delayed because of a residual but significant rivaroxaban activity. In the literature, a recent case report describes a lethal case of aortic dissection needing emergency surgical aortic repair in a 76-year-old man, with aneurysm of the descending aorta history, and anticoagulated with dabigatran. Despite haemofiltration, surgical revision and massive transfusion of packed blood cells, fresh frozen plasma, platelets, coagulation factors and recombinant factor VIIa, the patient died from intractable bleeding with sustained therapeutic levels of dabigatran.[1]

Conclusions: This case highlights the complex management of patients treated with direct oral anticoagulant therapy in emergency contexts given the absence of specific treatment option and especially antidote to reverse its anticoagulant effects. In this context, in cases of aneurysm or aortic dissection history, perhaps vitamin K antagonist should be preferred.

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Abstract Code: P-091

PRES Syndrome Induced by Cyclosporin with Normal Blood Concentration

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinico-neuroradiological entity. This syndrome is recognized in complex conditions as in allogeneic bone marrow transplantation, organ transplantation and with immunosuppressant drugs such as cyclosporin (CsA). The imaging, clinical and laboratory features of this toxic state are becoming better elucidated.

Case: A 26-year-old man received an allogenic bone marrow for bone marrow aplasia in January 2013. He was treated by CsA, methylprednisolone hemisuccinate, imipeneme, hemisuccinate sodique hexahydrate and amikacin. Mean CsA dose was 2.57 mg/kg/day. CsA mean blood concentration was 295 ng/mL (218–421 ng/mL). After 20 days, our patient had a complex partial seizure and cortical abnormal vision. CsA was stopped. He received mycophenolate acid and clonazepam. Seizure and abnormal vision disappeared 10 days later. Then, mycophenolate acid was stopped after 1.5 months and CsA taken back. CsA mean dose was 1.1 mg/kg/day. Mean CsA blood concentration was 167.71 ng/mL. After two months, the patient developed general seizures and on Magnetic Resonance Imaging (MRI) there was a low density in the subcortical white matter areas. So, CsA was stopped once and for all. Then seizures vanished.

Discussion and Conclusion: The incidence of PRES after allogeneic bone marrow transplantation using myeloablative marrow preconditioning and CsA immune suppression is approximately 7–9 % and appears to vary with a preconditioning regimen.[1] In vitro, studies have shown that CsA has a toxic effect on glial cells in culture and that the severity of the toxic damage was correlated with the duration of exposure.[2] In most cases, trough concentrations of CsA were supratherapeutic unlike our patient.[2] PRES occurs most commonly in the first month.[1] Our patient developed PRES after 20 days. PRES is responsible for various and non specific neurological symptoms such as confusion, coma, seizures and visual disturbances.[3] These symptoms are usually reversible but sometimes fatal.[2] The MRI frequently objectifies hypodensities at the subcortical white matter, mainly parieto-occipital. These brain lesions are commonly grouped under the name "leukoencephalopathy associated with immunosuppressants". [2]

So, therapeutic monitoring of CsA was necessary to avoid neurotoxicity that is dependent on concentration but we must remain cautious even if patients have CsA blood concentrations in the therapeutic range.

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Abstract Code: P-092

Cyclosporin Therapeutic Monitoring in Non-Infective Serious Uveitis

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Introduction: Cyclosporin A (CsA), a calcineurin inhibitor, is an immunosuppressant used especially in solid organ transplantation to prevent rejection. CsA can also be used in inflammatory diseases like non-infective uveitis. CsA is characterized by inter- and intra-individual pharmacokinetic variability. Therapeutic drug monitoring of CsA is indicated to avoid risk of inefficacity or toxicity.

Aim: To assess the interest of CsA therapeutic monitoring in case of non-infective serious uveitis.

Material and Methods: This was a retrospective study (January 2009–May 2014) conducted in the department of Clinical Pharmacology in patients treated with CsA for non-infective serious uveitis. Therapeutic drug monitoring was carried out by a chemiluminescent immunoassay.

Results: We collected 15 samples from 10 patients who were treated for serious non-infective uveitis. Patients' median age was 35 years and sex ratio was 1. The average weight was 34.8 kg. Patients were followed for an average of 2.4 years. Mean CsA dose was 3 mg/kg/day [1.85–4.28 mg/kg/day]. Mean trough blood concentration was 144.33 ng/mL and mean CsA peak blood concentration was 607.3 ng/mL. Neither of our patients had side effects.

Discussion and Conclusion: If uveitis is not resolved within 4 weeks of the use of high-dose (60–80 mg/day) oral prednisone or if no response is seen within 2 to 4 weeks of high-dose oral prednisone, an immunosuppressive agent should be added.[1] Recommended dose of CsA in non-infective serious uveitis is 3–5 mg/kg/day[2]. The CsA penetration is important in intraocular inflammation[1]. CsA leaves the vasculature readily and has been found in the intraocular fluids of patients treated for non-infective serious uveitis.[3]The inhibitory effect of CsA on uveitis may be partially mediated through inhibiting the production of IL-17 and IFN-γ.[4] The commonest adverse effects of CsA are hypertension and renal dysfunction, which are usually reversible if the drug is stopped. These adverse effects are concentration dependent.[5] So therapeutic drug monitoring is necessary in this population.

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Abstract Code: P-093

Feasibility of Pharmacist-Participated Anticoagulation Management Service (PAMS) in A Regional Hospital in Shanghai: A Pilot Study

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Introduction: The effectiveness of anticoagulation therapy is impacted by many factors including concomitant drug use, INR monitoring and patient factors. Pharmacist-participated anticoagulation management service (PAMS) has demonstrated effectiveness compared with routine medical care in various settings.[1–4] However, little is known about clinical and cost-effectiveness of PAMS in Shanghai, China.
Aim: To examine the feasibility and cultural adaptability of PAMS in a regional hospital in Shanghai.
Methods: A retrospective observational study of warfarin use and INR monitoring was conducted using patients' medical records from January 1st to April 30th 2014. In parallel, a telephone survey was administered in May 2014 by convenience sampling. Questionnaire items included patients' awareness, attitude and willingness to participate in PAMS. Basic expenditure on INR tests plus warfarin therapies for per patient-year was calculated and compared between patients who were willing to join PAMS and those who were not. Descriptive statistics and differences were compared using χ^2 test in SPSS 20.0.
Results: 206 patients were identified with 447 prescriptions of warfarin. 115 (55.8 %) patients attended the clinics for 241 INR tests. There was a significantly lower attendance rate among out-patients (45.7 % *vs.* 72.7 %, $P = 0.021$). Thirty (30/206, 26.1 %) patients achieved the target INR 2.0–3.0 (41/241, 17.0 %), while 91 (44.2 %) patients did not have a recorded INR test. Of all 37 (37/50, 74.0 %) sampled patients who consented to be interviewed, none had heard of PAMS but felt positive towards PAMS. Most patients (30/37, 81.1 %) were willing to participate in PAMS. The basic cost for per patient-year was RMB 203.6 CNY (32.3 USD). There was a 8.7 % cost reduction per patient-year (RMB 282.5 [44.8 USD] *vs.* 309.3 [49.1], $P < 0.001$) anticipated in the *PAMS* group *vs.* the usual care group.
Conclusions: This pilot study suggests that a considerable proportion of patients on warfarin therapy have suboptimal spot-INR levels in a single hospital in Shanghai. As patient acceptability of PAMS is positive, a cost effectiveness analysis will be useful to assess resource utilisation and compare the overall cost-effectiveness of PAMS *vs.* the usual care model.

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Abstract Code: P-094

Individual Risk Management Plans are Needed for Confident Biosimilar Prescribing

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Introduction: Biosimilar medicines are intended to have the same mechanism of action as the original biological medicines, and are designed to treat the same diseases as the innovator product. Unlike generic medicines where the active ingredients are identical, biosimilars are not likely to be identical to the originator biologic.
Aim: To address safety monitoring and the tools that should be refined in risk management plan of biosimilars for confident prescribing.
Method: Due to concerns about the comparability, similarity and safety of biosimilars, an individual risk management system is mandatory. Their pharmacological effect can be identical but their potential to cause adverse events might differ from the originator compound. An action plan for each potential safety concern must be provided.
Results: Post authorization safety studies are required for biosimilars and all observational safety information should be made public. Any safety monitoring imposed on the reference product or product class should be considered in their risk management plan. Validated sensitive antibody assays to detect immune responses, proper records to ensure traceability (the international nonproprietary name, INN), the brand name and batch number of the product should be mentioned during reporting in order to optimize therapy and reduce adverse effects.
Conclusions: Risk mitigation tools should differentiate between originator and biosimilar products so that effects of biosimilars are not lost in background of reports on reference products. The risk management plans for biosimilars must focus on enhanced monitoring measures, special safety reporting and implementation of post-marketing surveillance seems to solve thinking on its efficacy or safety risk.

Abstract Code: P-095

Varenicline and Abnormal Sleep-Related Events

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Background: Varenicline, a partial agonist to the α4β2 subtype of nicotinic acetylcholine receptors on neurones, is an aid to smoking cessation.

Abnormal dreams and unspecified sleep disorders were reported commonly in clinical trials of varenicline. Nightmares, somnambulism and aggression during wakefulness have been reported since marketing.[1,2] In the World Health Organisation (WHO) Global Individual Case Safety Report Database (VigiBase®)[3] the adverse drug reaction term "abnormal sleep-related event" appears in varenicline-related reports usually together with somnambulism, abnormal dreaming or nightmares. Since there were indications that these reports may represent harmful events we conducted a systematic assessment of the original versions of the reports that included this term.

Aim: To determine the nature of the reports in VigiBase® of "abnormal sleep-related events" associated with varenicline use.

Method: Original reports were requested from the four countries that contributed the reports. The reports were assessed to determine the nature of the abnormal sleep-related events.

Results: The 27 reports described patients who became active during sleep. Three groups of suspected sleep-related reactions were represented. Group 1. Ten patients became aggressive during sleep and actually or almost attacked their bed partners or others, usually in the context of violent dreams. No serious harm was inflicted but the events were frightening. Five patients described associated psychiatric symptoms and one re-activation of psychiatric illness. For seven patients, onset was within 3 weeks of starting varenicline. Seven patients recovered on discontinuing varenicline. Group 2. Seven patients engaged in non-aggressive harmful or potentially harmful activities associated with somnambulism and/or abnormal dreams. Four patients undertook normal activities made dangerous because they were asleep but two deliberately harmed themselves. Two patients recovered or were recovering on discontinuation of varenicline. Group 3. The remaining 10 reports described non-harmful sleep activities. However, four involved frightening experiences, one patient pulled down wall fixtures. Across the three groups psychiatric illness, alcohol use, statin use and hypoxic disorders were described sporadically but there was no clear alternative to varenicline to explain the events.

Discussion/Conclusion: The reports examined reveal that the ADR term "abnormal sleep-related event" when associated with varenicline use frequently represented harmful or potentially harmful activities often occurring in the context of disturbing dreams, nightmares and/or somnambulism. The reports are not in keeping with descriptions of tobacco withdrawal.[4] The reports of aggression are similar to a rare parasomnia known as rapid eye movement (REM) sleep behaviour disorder.[5]

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Abstract Code: P-096

Reporting of Adverse Drug Reactions by the End Users—Patients in Pakistan

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Aim: To assess the feasibility of involving end users in reporting and monitoring the suspected adverse drug reactions (ADR's) in Pakistan, a household survey was carried out in three major cities of Punjab, Pakistan namely Lahore, Rawalpindi and Multan using a pre-tested questionnaire. Responses were obtained from a total of 1566 households in three cities together. Also elicited were the opinions of other stakeholders such as (a) hospitals and nursing homes, (b) private medical practitioners, (c) chemists/druggists, with regard to involving households in the reporting of ADRs. A huge around 93 per cent of the households are willing to report ADRs. The stakeholders are also in favor of involving end users—the patients in the reporting of ADRs and believe that it is a good idea. It is concluded that in cases where an ADR is likely to occur, an ADR form may be given to the end users at the time of prescribing by doctors or of dispensing by chemists/druggists. A prepaid system of providing an inland letter/stamped envelop is a feasible option for encouraging end users—the patients to report the ADRs experienced by them.

Introduction: National pharmacovigilance programme of Pakistan to monitor Adverse Drug Reactions (ADR's) and help to improve the safety of medicines recently prescribed by the drug regulatory authority of Pakistan. Under-reporting is the major concern in national pharmacovigilance programme, especially those dependent on spontaneous reporting.

Methods: Three cites in Punjab-Pakistan, namely Lahore-Rawalpini and Multan (three diverse and well populated cities of Pakistan) were selected for this study. In each city, three towns were selected at random. A total of 1566 households were interviewed between February and April 2014. About 58 % are from rural areas while 42 % of the households are from urban areas.

Conclusions: All over the world there is an increasing trend of involving end users—the patients in the process of health care. Consumer reporting has several advantages like qualitative and quantitative details; increase in ADRs reported, newer ADRs being reported, early detection of ADRs and also as a strategy to prevent medication errors.

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Abstract Code: P-097

Experience of Implementation of Risk Management Plans in Argentina

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Introduction: Risk management plans (RMP) were first required by a communication act in 2009 and its legislation come into force in 2013 with the Good Pharmacovigilance Practices (Disposición ANMAT 5358/12). As a consequence, in the recent years, stakeholders submitted many RMPs with new approaches to demonstrate drug safety and to prevent adverse drug reactions (ADR).
Aim: To describe the characteristics of the submitted RMPs. To assess the RMP execution fulfillment by stakeholders.
Methods: We reviewed the RMP and ADR data bases of the ANMAT Pharmacovigilance Department, from 2009 to 2013. We reviewed the marketing status of medicines in the official list of currently marketed medicine products.
Results: Since 2009, the ANMAT Pharmacovigilance Department approved 148 RMPs corresponding to 102 drug substances. Each RMP is concerned with one medicine product. The intensive monitoring programs of thalidomide and clozapine, existing since 1996, were included in the RMPs. The submission reasons were: new active substances: 87; special licensing: 10; novel association of active substances: 9; biosimilars: 9; significant changes in the medicine products: 6; request of regulator/new safety concerns: 27. The RMPs encompassed the following activities: follow-up questionnaire of certain ADRs: 40; proactive pharmacovigilance; 46; clinical trials: 42; sentinel sites: 6; patient registries: 20, educational materials for healthcare professionals: 71; educational materials for patients: 32; legal status of the medicine/controlled distribution: 26; pregnancy prevention plans: 8; informed consent: 20. At the time of this presentation, 126 medicine products were on the market and 124 of them were in term to submit a RMP report. The Pharmacovigilance Department evaluated reports from 57 (45.9 %) products in that condition. The Pharmacovigilance Department received ADR reports of 80 (63.5 %) medicine products under RMP.
Conclusions: The tools implemented to manage the drug safety were diverse and were based on local reality. The quality of submissions improved as the companies and the regulator gained experience in RMP. Although not optimal, there was a high degree of compliance in the implementation of the RMPs. The ANMAT Pharmacovigilance Department assessed at least one RMP report from almost half of the products that were in term of presentation of that report and received ADR reports from more than the half of the marketed medicine products under a RMP. The next phase of the review will be to audit effectiveness of measures contained in a RMP.
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Abstract Code: P-098

New Biomarker for Developing Adverse Drug Reactions Caused by Statins

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Background: Newly identified risk factors for statin induced toxicity are genetic variants of drug metabolizing enzymes and membrane transporters. For simvastatin, the evidence linking myopathy and *SLCO1B1* 521 T>C is strong, and this association has been reproduced in randomized trials and clinical practice-based cohorts. The Clinical Pharmacogenomics Implementation Consortium developed Guideline for *SLCO1B1*and Simvastatin-Induced Myopathy.[1] The association of *SLCO1B1* 521 T>C with myopathy has been less compelling for other statins.The ABCG2 efflux transporter is expressed in multiple tissues and plays an important role in the disposition of different drugs including statins. The functional 421C>A polymorphism in the ABCG2 that reduces transporter activity has been found to be associated with increased systemic exposures to statins[2]. Data about influence of this variant on developing Adverse Drug Reactions (ADRs) caused by statins is less well known. In our previous work we show an association between fluvastatin induced ADRs in renal transplant patients and genetics variants in the *ABCG2* and *CYP2C9* gene.[3]
Aim: The aim of this study was to show the contribution of ABCG2 gene variant to the development of dose-related statin ADRs.
Patients and Methods: We did case–control study. 187 patients were included in the study; 60 patients with ADRs to atorvastatin therapy, 50 patients with ADRs to simvastatin, 52 patients with ADRs to fluvastatin therapy and 25 patients with ADRs to rosuvastatin therapy and 187 controls without ADRs (matched according to statin dose, age, gender, concomitant therapy). Genotyping of the ABCG2 421C>A polymorphism was performed using the TaqMan allele-specific PCR assay (AppliedBiosystems).
Results: Most ADRs were caused by myotoxicity of statins: 90.4 % of fluvastatin ADRs, 68 % of simvastatin ADRs and 56.7 % of atorvastatin ADRs and 52 % of rosuvastatin ADRs. We found a statistically significant difference in the frequency distribution of ABCG2 421 C>A genotypes between patients with adverse drug reactions and controls: fluvastatin group *ABCG2* 421C>A ($\chi^2 = 8{,}559$; df = 2; p = 0,014; Cramerov $\varphi = 0.29$), atorvastatin group ($\chi^2 = 7{,}222$; df = 2; p = 0,015; Cramer's $\varphi = 0{,}245$) and subgroup of patients that developed miotoxicity caused by simvastatin ($\chi^2 = 5.477$; df = 2; p = 0.039; Cramer's $\varphi = 0.260$).
Conclusion: We found out that A allele carriers of *ABCG2* 421C>A (421CA and 421AA genotypes), responsible for reduced transport function, were at greater risk for developing dose-related ADRs to atorvastatin, simvastatin, fluvastatin and rosuvastatin therapy compared to non-carriers of this polymorphism. This is the first study showing that variants of ABCG2 are predictor of statin ADRs.
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Adverse Drug Reactions Caused by Hepatoxicity of Drugs Reported to Agency for Medicinal Products and Medical Devices

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Introduction: Drug-induced liver injury (DILI) is an important health problem. DILI is the one of main reasons for withdrawal of drugs from the market. There is no biomarker that is specific and sensitive enough to distinguish DILI from other causes of liver injury. Initiatives to improve the identification of adverse hepatic reactions and to find reliable information about the epidemiology and pathogenesis are being made worldwide.

Methods: We analyzed Adverse Drug Reactions (ADRs) reported to the Agency for the period from January 2005 to December 2013 belonging to the MedDRA System Organ Class: Hepatobiliary disorders or High level group term: Hepatobiliary investigations.

ADRs were evaluated according to their seriousness. All ADRs which resulted in death or were life threatening, required inpatient hospitalization/prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, a congenital anomaly/birth defect or were other important medical event were labeled as serious. We also analyzed ADRs caused by hepatotoxicity according to gender and age distribution.

Results: In the analyzed period, 360 reports contained ADRs belonging to Hepatobiliary disorders or Hepatobiliary investigations. 51 % of all patients in the study were females. Most patients belonged to the age group 45–64 years (33 %), followed by the age group 18–44 years (30 %).

We found that 76 % of all reported ADRs caused by hepatotoxicity were caused by drugs from ATC group N (34.7 %), C (26.2 %) and J (15.1 %). Among drugs belonging to the ATC group N, antiepileptics were most often reported as suspected drugs, especially methylphenobarbital (n = 36), followed by carbamazepine (n = 25) and oxycarbamazepine (n = 23). Most of the serious ADRs were associated with drugs belonging to ATC group C (36.4 %). This could be explained by the high proportion of ADRs reported to statins and cases of myopathy and rhabdomyolysis with elevated liver enzymes.

Conclusion: Results of this analysis can help as to better plan pharmacovigilance activities.

Abstract Code: P-100

Characteristics Legal Warnings after Drug Approval: Retrospective Review of Drug Risk Management in Thailand

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Introduction: There are many tools of drug risk management (DRM) for minimizing risk and black-boxed warnings (BBWs) are one of those tools.[1] Some serious adverse drug reactions (ADRs) emerge only after a drug is marketed and used in a larger population.[2,3] Boxed warnings have been a long-standing feature of safety regulation of medicines in developed countries, but there has been no information about the frequency or

Table I Characteristics of safety trigger caused legal warning change in Thailand 2003–2012

Year	Drug class	Drug name	First safety trigger
2003	Fluoroquinolones	Ciprofloxacin Ofloxacin Norfloxacin Moxifloxacin	Serious skin reactions reported in Thailand and other countries
2006	Conventional NSAIDs	Diclofenac Ketoprofen Piroxicam Meloxicam Tenoxicam Ibuprofen	Revision of all NSAIDs due to referral of some COX-2 inhibitor drug class in the US
2006	Selective COX-2 inhibitors	Celecoxib Parecoxib Etoricoxib	Removal of some COX-2 inhibitor drug class in the EU
2006	Hormone replacement therapy	Estrogen or estradiol and progesterone or progestin	Report of serious thromboembolism in Canada, Australia and the US
2007	Nimesulide		Suspension in Ireland from liver toxicity and review of benefit and risk in the EU
2007	Thiazolidinediones	Rosiglitazone	Report of serious cardiovascular events in Canada and the US
2011	Thiazolidinediones	Pioglitazone	Report of bladder cancer in France
2011	Sulfonamides	Sulfasalazine	Market authorization holders asked for change of teratogenic class effect in Thailand due to the adjustment of safety profile
2011	Sulfonamides	Sulfadiazine Sulfadoxine Sulfafurazole Sulfamethoxazol	Review of teratogenic class effect in Thailand due to the adjustment of safety profile
2011	Statins	Simvastatin Fluvastatin Cerevastatin Atorvastatin Pravastatin	Change of safety information about cardiovascular events in the EU

nature of the use of boxed warnings in South-East Asian countries. In Thailand, additional legal-warnings after drug approval, in the form of black-boxed warnings, have been applied. Review of their characteristics can assist in the development of effective risk mitigation.

Aim: To identify the criteria or category of risks in legal warnings in Thailand in the post-marketing phase. The specific characteristics of warnings after drugs approval were evaluated. Additionally, the triggers of legal warnings were also assessed.

Methods: We performed a cross-sectional retrospective review of all legal warnings imposed in Thailand after drug approval (2003–2012). Any boxed-warnings for biological products and revised warnings which were not related to safety were excluded.

Results: Nine legal-warnings were evaluated. Seven related to drugs classes and two to individual drugs were included in the reviewed details in Table I. The warnings involved four-main types of predictable ADRs: (1) drug-disease interactions, (2) side effects, (3) overdose and (4) drug–drug interactions. The triggers were from both safety signals in Thailand and regulatory measures in other countries. The average time from first ADRs reported to legal warnings implementation was 12-years.

Conclusions: Compared with previous literature, these results are consistent. Although the timings of implementation of new box warnings in other studies were analysed by different methods, the emergence of safety signals in surveillance systems were similar important triggers for action. The study shows that in Thailand to date the imposition of legal warnings has been largely limited to serious safety concerns identified internationally and about which other major regulatory agencies have also taken action.

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Abstract Code: P-101

Anticancer Drugs' Side Effects

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Introduction: Anticancer drugs (AD) lead to improve the survival of cancer patients. However, these drugs are characterized by several side effects affecting quality of life and treatment adherence.

Aim: The aim of our study was to report side effects of AD and to analyze their epidemiologic characteristics.

Methods: This is a retrospective study about all AD side effects cases notified to CNPV from January 2011 to December 2012. The Begaud's Method was used to assess the imputation between drugs and side effects. We retained all cases with an imputation score of the AD equal or superior to the imputation score of other associated drugs. We obtained 88 cases. Exclusion criteria were: an incompatible chronology, another etiology retained, an imputation score of AD inferior to that of associated drugs, an indication of AD prescription other than cancer. We retained 29 cases.

Results: The age of patients varied between 12 and 88 years; 62 % of patients were between 30 and 60 years. The sex ratio F/M was 2.62. The main indication of AD was breast cancer (n = 10). Among the side effects retrieved, 23 were mucocutaneous including 2 cases of psoriasiform eruption, 2 cases of eczematifrom eruption and 3 cases of palmar-plantar erythrodysesthya (PPE), 11 were general manifestations (fever, dizziness, hot flushes, oedema, joint pain), 5 were digestive. The most reported drugs were docetaxel (n = 10), cyclophosphamide (n = 6), etoposide (n = 6), 5 fluouracile (n = 4) and oxaliplatine (n = 4). 82,5 % of drugs were originators. The imputation score was I3 (likely) in 4 cases, I2 (possible) in 14 cases and I1 (doubtful) in 11 cases.

Conclusion: In our serie, we noted a feminine predominance in line with literature data. Side effects were mainly mucocutaneous. Among them, we observed 2 cases of psoriasiform eruption to imatinib, 2 uncommon cases of eczematous eruption associated with docetaxel and 3 cases of PPE also dealing with docetaxel administration. In literature, imatinib and docetaxel are known to induce respectively psoriasiform eruption and PPE; however, eczematous eruptions are not reported with docetaxel. In this serie, docetaxel was the most reported drug; in fact, it is prescribed in breast cancer which was the main indication in our serie. Drugs were mainly originators, this is probably related to the little number of AD generics in Tunisia; and to a lower prescription of generics by clinicians because of their belief that they are more toxic.

Abstract Code: P-102

Duplicated Case Reports of Stress Cardiomyopathy: Implications for Signal Detection

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Introduction: Duplicated case reports can be an important issue in safety signal detection. The potential impacts (e.g. false positive and negative findings) can be 'extreme' despite use of duplicate detection algorithms in proprietary software.[1] Herein we describe what appears to be another example of 'extreme duplication' in the US FDAERs data base discovered in the course of our real-world signal evaluation activities Specifically we discovered numerous duplicated case reports of stress cardiomyopathy (Tako Tsubo cardiomyopathy)[2] in the evaluation of a signal of this drug-event combination (DEC).

Method: The US FDA Adverse Events Reporting System (FAERS) database was searched and all cases with the drug of interest that reported adverse events encoding to MedDRA (version 16.0) Preferred Terms (PT) Stress cardiomyopathy received through 27 August 2012 were obtained via a Freedom of Information (FOI) request. For each case, the following information was extracted: event (date, PT, System Organ Class, High Level Group Term, High Level Term), case (ISR#, age, gender, report code, seriousness, country), medication (generic name, trade name, indication, start and end date, dose, route of administration, manufacturer, manufacturer number, dechallenge and rechallenge), outcome (recovered, death, life threatening, hospitalization, required intervention, disability and other), source (health professional, consumer, literature, clinical study, regulatory agency, foreign, other) and case narratives. The above information was reviewed to search for duplicated reports based on demographic characteristics, country of origin, reported PTs and case description. Manual review was complemented by univariate and

multivariate statistical analysis to visualize the distribution of variables pertinent to duplicate detection. The impact of this report duplication on disproportionality analysis (DA) was assessed.

Results: There were 40 stress cardiomyopathy cases. After detailed manual review and univariate and multivariate statistical analysis of the aforementioned variables more than 60 % of the cases were considered be duplicated. Characteristics of spontaneous reports that predispose to extreme duplication will be discussed. Potential impact of this level of duplicate reporting on measures of disproportionate reporting are significant.

Conclusion: Duplicate reporting, which can escape detection algorithms, can impact signal detection e.g. false positive and false negative findings, depending on various factors (e.g. overall distribution of duplicates in the database, ease of duplicate identification). Investigators should review all information to identify potential duplicates. Univariate and multivariate statistical analysis can support duplicate detection by helping to visualize patterns of relevant variables.

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Abstract Code: P-103

How the Transparency Data Regulations are Changing the Communication Regarding Benefit-Risk of Medications

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Background: Access to Regulators documents is effective for post-marketing data i.e. PSURs, RMPs; and under evaluation for clinical trials. A broader release, earlier, to a broader audience and its impact on safety messages are debated.

Objectives: To highlight the changes occurring/transforming the landscape of Risk-Benefit communication following recent regulations from FDA and EMA on pharmaceutical data Transparency from the Pharmaceutical Companies perspective publishing these clinical research and safety information, to the patients and physicians receiving them.

Methods: Literature analysis and Pharmacovigilance stakeholders feedback.

Results: Requests for post-marketing safety data range from toxicology reports to PSUR and Risk management plans, mainly from the pharma industry and lawyers. The information released is received with mixed feedback, too early for the prescribers, and mixed for patients. These requests create cumbersome, delicate processes for Pharmaceutical Companies without necessarily benefiting the Patient. As for clinical trials data, although accepted in principle, differences on implementation exist between Regulators, EMA especially on its Policy 70 and PhRMA/EFPIA Pharmaceuticals associations. If the Drug Industry is reluctant to disclose all clinical data, how about the investigators helping them gathering the information, the patients reporting outcomes directly from their smart phones to the Companies database? With the Patient's voice heard at PRAC, FDA consultation, or BRACE and at the age of news going viral around the globe in seconds, innovative and collaborative ways of data sharing among PV stakeholders are inevitable and beneficial to the Patient.

Conclusions: The commitment to proactively publish data from clinical trials and from post-marketing was anticipated to re/establish trust and confidence in the System. Although this will need further evaluation, the principle of releasing this data is accepted. The agreement on the magnitude of the data release and when it occurs is still being debated. Innovative ways to communicate Risk-Benefit information are on the rise, and changing the landscape of traditonal Pharmacovigilance.

Abstract Code: P-104

Therapeutic Drug Monitoring in the Treatment of Tuberculosis: Minimizing the Risks of ADRs

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Introduction: Adverse drug reactions (ADRs) of anti-TB drugs (ATBs) are frequent. According to previous studies, around 14 to 15 % patients developed ADRs to isoniazid and rifampicin. [1–4]. These ADRs are usually mild but sometimes became fatal. These days therapeutic drug monitoring (TDM) is a useful technique to prevent and minimize such ADRs of ATBs. This study is a first of its type as such work has not been previously undertaken in Malaysia.

Aim: To evaluate the usefulness of TDM to prevent and minimize ADRs of ATBs in Malaysia.

Methods: A retrospective study was conducted to analyse time interval pattern and duration of the TDM analysis performed on isoniazid and rifampicin in a TDM-unit in a tertiary hospital between January 2012 and December 2013. The TDM of isoniazid was done after 3 h of its first administration while TDM for rifampicin was done after 2 h of its first administration. A descriptive analysis of the ADRs of both ATBs was observed and correlation of ADRs with plasma drug concentrations was discussed. All obtained data were analysed using descriptive and inferential statistics.

Results: According to the data obtained, a total of 74 out of 168 studied patients experienced ADRs. The TDM of isoniazid showed that a proportion of 78.8 % (n = 61) of its plasma concentration was higher than its official recommended dose (1–2 mg/l), while only 21.2 % (n = 13) was within the recommended efficient dose. On the other hand, the TDM of rifampicin showed that a proportion of 70.3 % (n = 52) of its plasma concentration was higher than its official recommended dose (6–12 mg/l), while only 29.7 % (n = 22) was within the recommended efficient dose. The most serious and severe noted ADRs were liver and biliary disorders which presented around 81 % of the other minor ADRs experienced by the patients.

Conclusions: Both ATBs plasma levels were higher than their clinically acceptable levels in patients with active TB which ultimately potentiated

severe ADRs. TDM is highly beneficial for the treatment of active TB, but mostly it is underused. TDM allows individual adjustment of the doses of the drugs to be taken by the patients to minimize the potential risks of ADRs.

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Abstract Code: P-105

Drug-Induced Gynecomastia

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Introduction: Gynecomastia is the first breast disease in males. It is generally caused by endocrinological or tumoral etiologies. Drugs are estimated to cause about 10–25 % of all cases of gynecomastia.[1] Many drugs are involoved in this manifestation such as neuroleptics, spironolactone, sexual hormones (anti-androgens, 5 α-reductase inhibitors)

Aim: To identify drugs associated with gynecomastia reported to pharmacovigilance.

Methods: This was a retrospective study. We analyzed all the cases of drug-induced gynecomastia notified to the Pharmacovigilance Centre for the period from January 2009 to December 2013. The assessment of imputation between drugs and gynecomastia was evaluated by the Begaud's method.

Results: Five cases of gynecomastia were found. The median age of patients was 46 years (38–64 years). The gynecomastia was unilateral in 4 cases and bilateral in one case. The drugs retained as possibly responsible of this gynecomastia were atenolol (score = I2), sertraline (score = I1), isoniazid (score = I1), oxetorone (score = I2) and amitryptyline (score = I1). The outcome was favorable in one patient 3 months after the withdrawal of the drug (oxetorone); in the other cases, the outcome could not been evaluated because it was slow, and because the drug could not been stopped.

Conclusion: Over the period of 5 years, only 5 cases of gynecomastia were notified to CNPV. This emphasizes the under-reporting of this trouble. In our series, the drugs associated with gynecomastia are rarely reported to induce this trouble in literature. The difficulty in these cases was to evaluate the evolution of gynecomastia which is generally slow, that made it difficult to assess imputation especially as some essential drugs could not been stopped.

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Abstract Code: P-106

Drug-Induced Acute Pancreatitis

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Introduction: Acute pancreatitis (AP) is an inflammation of pancreas up to a destruction of pancreatic tissue. Its most common etiologies are gallstones and alcoholism. Rarely, it can be induced by drugs. The drug-induced acute pancreatitis represents about 2 % of all acute pancreatitis.[1]

Aim: To study epidemiological and clinical features of pancreatitis cases notified to pharmacovigilance.

Methods: This is a retrospective study about drug-induced acute pancreatitis cases notified to Pharmacovigilance Centre for a period of 5 years from January 2009 and December 2013. The Begaud's Method was used to assess the imputation between drugs and AP. We retained all cases with an imputation score different from I0. We excluded cases where another etiology was identified.

Results: >We retained 30 cases. The median age of patients was 50 years [13, 84]. The sex ratio M/F was 0,76. The amylase rate averaged 2 N. The CT scan was specified in 12 cases (stage A (n = 1), stage B (n = 2), stage C (n = 2), stage D (n = 4), stage E (n = 3)). The number of drugs suspected in each case has varied between 1 to 10 drugs. The most reported drugs were meglumine antimoniate (n = 7), azathioprine (n = 6), furosemid (n = 5). In 13 cases, only one drug was suspected mostly meglumine antimoniate (n = 7) and azathioprine (n = 2). The mean delay was 2 years and 6 months [1 day, 15 years]. The outcome was favorable in 21 cases: in 17 cases, after the drug withdrawal and intake of symptomatic treatment and in 4 cases despite continuing the treatment.

Conclusion: The assesment of the imputation between drugs and the pancreatitis was difficult to establish given the long delay (averaged over 2 years) and often imprecise or slow outcome. Thus, the imputation score was moreover evaluated between I1(doubtful) and I2(possible). The main drugs associated with AP were meglumine antimoniate, azathioprine and furosemid.

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Abstract Code: P-107

Sexual Disorders Associated with Drugs

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Introduction: Sexual disorders (SD) affect significantly the family life of individuals and their psychological condition. These troubles are manifested by frigidity and vaginismus in women; by erectile dysfunction, premature ejaculation and anejaculation in men. Drugs are among the etiologies of sexual disorders such as vasodilators, antihypertensive drugs, psychotropic drugs.

Aim: To report cases of SD notified to pharmacovigilance.

Methods: This is a retrospective study about SD cases notified to Pharmacovigilance Centre for a period of 5 years from January 2009 and December 2013. We excluded cases of secondary sex characteristics.
Results: We retained 3 cases. All three were male. They were aged 46,38 and 51 years old. In the first case, the patient developed a premature ejaculation. The drugs which remained suspected were methotrexate, amlodipine and famotidine; the delay was respectively 5 years, 5 years and 1 month. In the second case, the patient developed a loss of libido which was associated with carbamazepine intake; the delay was 6 months. In the third case, the patient developed an erectile dysfunction. The methotrexate was retained as responsible of this trouble; the delay was 6 months.
Conclusion: This study allowed us to identify only 3 cases of SD during these last 5 years. This number is too little compared to what it is expected seen in literature data. Also, the 3 cases were males. These facts are probably due to taboos surrounding the sexuality in our society and the difficulty to reveal these troubles especially in women. In 2 cases over 3, methotrexate was involved in SD onset. In literature, this drug is known to induce erectile dysfunction and loss of libido.

Abstract Code: P-108

From the Unknown to Current Practices of Pharmacogenomics

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The DNA code has been cracked, and with it an immense field of opportunity to better understand adverse drug reactions and even better prevent them, has been opened. As the awareness to the benefits rises, the fear of using these tools is diminishing. Their benefits have already been demonstrated and the Health Authorities have prepared regulations on their usage. In this session, the authors will cover the following concepts: overview of genomics, phenotype and pharmacogenomics, current regulations and guidelines from EMA, FDA and ENCPP, presentation of patient stories and successful labeling update with pharmacogenomics helping understand the reasons for adverse drug reactions and therefore how to prevent them, "living" the personalized medicine concept. Finally, reflecting on recent PRAC and FDA request, the authors will open up the debate to the future next steps for Pharmacovigilance.

Abstract Code: P-109

Initiation and Evaluation of Patient Reporting ADRs in Out-patient Department of a Tertiary Care Hospital in India

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Introduction: Adverse Drug Reactions (ADR) are among the leading causes of morbidity and mortality. Many developed countries consider patients as active members in the disease management, including ADR reporting. Patients are the key elements in tracking the information about the ADR in Post Marketing Surveillance (PMS). Patient reporting of suspected ADRs has the potential to increase the knowledge about the possible harm of drugs.
Objective: To initiate & evaluate Patient reporting of suspected ADRs in an ambulatory care setting.
Methodology: A prospective observational study was conducted in the Out-patient of General Medicine department of a tertiary care hospital over a period of 6 months. On obtaining the informed consent the patients were explained about the prescribed medications and were trained to identify and report any unusual symptoms to the research investigators. On receiving call the investigator obtained all necessary information by interviewing the patient and were recommended to physician for further action. The collected data was analysed for establishing causality and type of reaction, outcome and fate of the suspected drug were assessed. Descriptive statistics, T-test and Chi Square test were used to perform the analysis.
Results: During the study period, 1125 patients were enrolled of which 128 patients called back reporting 95 ADRs [response rate 8.44 %]. The mean age of the study population was 50.14 % $\pm$ 16.39 years. The number of females [54 (57 %)] reporting ADRs was found to be higher than males [41 (43 %)] [P = 0.001 Sig.]. Maximum number of reports were obtained from patients in the age group of 40–60 [38 (40 %)]. It was also observed that the number of reports were more as the education was higher [UG 38.8 %]. GI Disorders [34 (35.78 %)] and Skin & Appendages [22 (23.10 %)] comprised majority of experienced ADRs. A comparison of the Modified Hartwig& Siegel plot of patient reported ADRs with that of Physician reported ADRs reveals that health professionals report mainly Moderate (57.57 %) reactions in contrast to patient reports which included Mild reactions more often (66.15 %) [T-test (0.986)].
Conclusion: Patient reporting ADRs is a valuable tool in Pharmacovigilance. Patient reports are comprehensive in describing all the necessary Pharmacovigilance data. Findings suggest that sensitizing the patients improve patient reporting. Patient reporting can strengthen the Pharmacovigilance of a country working synergistically in identifying and reporting ADRs thereby resulting in a safer medication use experience.

Abstract Code: P-110

Risk Management and Pharmacovigilance in the Brazilian Health Surveillance Agency: The Benzydamine Case

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Risk management of drugs is defined as a set of activities and interventions designed to identify, characterize, prevent or minimize risks relating to the use of medicines, including monitoring the effectiveness of these activities. It is a very important issue on pharmacovigilance context and aims to maintain a positive balance between the benefits and risks associated with the use of these health technologies. This paper presents the activities related to risk management at Brazilian Health Surveillance Agency (ANVISA) using the case of benzydamine as an example of a full benefit/risk assessment of a drug performed by Pharmacovigilance Office. The benzydamine hydrochloride is a non-steroidal anti-inflammatory drug. In Brazil, the drug was registered in dosage forms of topical and systemic use. In July 2013, a doctor reported a case of benzidamine abuse by a patient. The abuse of the drug for systemic

use has led the patient to a serious crisis of hallucinations and delirium that led to a suicide attempt. Considering the importance and seriousness of the case, the pharmacovigilance team started a process of safety drug review. Initially, we carried out a search in adverse events databases routinely accessed by the Pharmacovigilance Officer. In 89.2 % of 65 reports received from 2003 to 2013, there were problems related to the substance use, characterized as administration errors or drug misuse. In 3 % of cases, it was reported the recreational drug use in association with alcohol. Other databases were consulted in order to strengthen the safety signal, such as Vigibase (The Uppsala Monitoring Centre database) and the Toxicological Assistance Center from São Paulo University (CEATOX). CEATOX reports drew attention due to two suicide attempts and three suicides that may be related to the use of the benzydamine. In addition to the reports received, we performed a search on scientific literature and the internet (where virtual communities encouraged substance abuse). Moreover, ANVISA analysed the benzydamine Periodic Safety Update Report (PSUR). [1,2] The PSUR review corroborated the hypothesis of safety profile change. Based on the presented survey, ANVISA identified a change in the benzydamine benefit / risk relation and ordered the authorization withdraw of the systemic use pharmaceutical form, considering the identified risks and the existence of alternative therapies on the Brazilian market.

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Abstract Code: P-111

Drug Induced Liver Injury Caused by Herbal Drugs and Dietary Supplements

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Liver injury is a rare, unpredictable idiosyncratic adverse reaction of drugs, herbal drugs (HD) and dietary supplements (DS).[1] In developed countries, Drug-Induced Liver Injury (DILI) is a leading cause of acute hepatic failure (HF) [2], while in Asian countries DILI is more often caused by 'herbs' and dietary supplements (HDS). [3] The popularity of herbal products has increased over the past decade, particularly among women and elderly patients who are at increased risk for liver injury.[4] In the World Health Organization database, VigiBase™, 69.92 % of hepatotoxicity cases caused by herbal dietary supplements occurred in women (69.92 %; females-258 vs. males-96; $p < 0.001$).[5] Because they are rare or very rare and unpredictable, hepatic reactions are mainly detected during post-marketing drug monitoring, when significant patients' exposure is achieved. Spontaneous reporting of adverse drug reactions is of great importance for the identification of unexpected DILI cases. HDs are frequently used in combination with prescription and over the counter medications, which increases the risk for drug interactions. Updated data from international DILI registries suggest that hepatotoxicity in the elderly appears to be due to drug exposure, polypharmacy and drug–drug interactions.[6] This presentation aims to point out the potential harmful effect of DS and herbal DS and the relevance of spontaneous reporting of adverse effects associated with DS use. Herbal supplements that have been associated with hepatotoxicity (Herbalife, LipoKinetix, supplements that contained Pirazolidina alkaloids, germander, root Cimicifugae racemosae) will be discussed.

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Abstract Code: P-112

Serious ADRs Analysis in Old People Aged Over 65

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Background: National ADR center received nearly 1.32 million ADR reports in 2013, of which old people aged more than 65 (hereinafter referred to as old people) accounted for 17.8 %. Among serious ADR reports of this year, old people reports acounted for 25.3 % and the proportion in serious cases increased significantly.
Objective: To summarize the characteristic of serious ADRs among old people and provide safe medication guide for this age group.
Methods: Serious ADR reports in old people received by National Center in 2013 were analysized according to general information, medicine, ADR etc and compared with the overall.
Results: In 2013, there are more than 223,000 ADR reports in old people, of which nearly 14,000 ADR reports (6 %) are serious and it's higher than the whole people's proportion (4.3 %). Among serious ADR in old people this year, male and female ratio was 1.19:1; the reports in age group 65–74 accounted for 56 %, followed by age group 75–84 contributing about 34.2 %; referring to medicine, chemical medicine and biological products accounted for 84.0 %, the others(16.0 %) were traditional Chinese medicine(TCM) whose proportion was higher than the overall's(11.9 %); among top ten chemical medicine and biological products, anti-infectious agents were in the first place, which respectively

were Levofloxacin, Ceftriaxone, Cefoperazone/ Tazobactam sodium, Penicillin, Piperacillin/Tazobactam sodium, followed by antineoplastic medicine (Paclitaxel, Docetaxel), nutriceutical medicine(Compound Amino Acid), Cardiovascular medicine (Aspirin); in terms of chemical medicine and biological products' ADRs, general disorders(26.9 %), respiratory disorders(13.3 %) are mainly involved organ and systems, for instance, anaphylactic shock, chills, breathing difficulties, chest distress, anaphylactic reaction; among TCM, injections contributed for 92.0 % and most of ADRs were related to general disorders(37.6 %), respiratory disorders(23.0 %), such as, breathing difficulties, chest distress, anaphylactic reaction, hyperpyrexia.

Conclusions: Over 65 old people were needed to pay attention to serious ADRs related to anti-infectious agents, antineoplastic medicine, TCM injections, etc. and should be designed more rational dosage regimen. Serious ADRs are featured with acute allergic reactions, so should be monitored well in early medication stage.

Abstract Code: P-113

Pharmacovigilance with Special Focus on the Geriatric Patients at a Public Teaching Hospital

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Introduction: Adverse drug reactions (ADRs) in older adults are an important healthcare problem since they are frequently a cause of hospitalization, occur commonly during admission, and are an important cause of morbidity and mortality. Older adults are particularly susceptible to ADRs because they are usually on multiple drug regimens and because age is associated with changes in pharmacokinetics and pharmacodynamics.[1]

Aim: To identify most commonly occurring ADRs in older adults and to determine the causality, severity and preventability of adverse drug reactions.

Methods: A prospective observational study was conducted in three general wards of medicine department of a public teaching hospital. All relevant information was collected from patients' record files. The information included reason and date of admission in hospital, date of discharge, drug allergies, diagnosis and co-morbid conditions. All prescribed drugs including dose, frequency and route of administration were recorded.

Assessment of ADRs was performed with the help of standardized scales. For causality, two different scales were used. The scales were Naranjo's ADR probability scale and WHO-UMC causality categories. ADRs were classified into mild, moderate and severe reactions using the Modified Hartwig's severity scale for severity assessment. By using the modified Schumock and Thornton's criteria, ADRs were classified into definitely preventable, probably preventable and not preventable.

Results: Data of 1460 patients were captured and analyzed. A total of 46 ADRs were identified in 44 older adults, giving an incidence of 13 %. The top three most common adverse drug reactions were diarrhea (15), constipation (10) and hypokalemia (9) respectively. The drugs responsible for causing these ADRs were ceftriaxone, metronidazole, ofloxacin, piperacillin + tazobactum, tramadol and furosemide. About 50 % of the ADRs were reported by ceftriaxone alone.

According to Naranjo's ADR probability scale, 35 % ADRs were 'possible' and 65 % ADRs were 'probable'. WHO-UMC causality scale showed that 44 % ADRs were 'probable' and 56 % ADRs were 'possible'. Severity assessment, using Modified Hartwig criteria, showed that 61 % ADRs were mild and 41 % ADRs were moderate respectively. Preventability of ADRs was assessed using modified Shumock and Thornton method; and, it was found that 59 % ADRs were not 'preventable' and 39 % ADRs were found to be 'Probably preventable'.

Conclusions: This study concluded that the diarrhea was found to be the most common ADR. No severe harm to the patients was found.

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Abstract Code: P-114

Distribution of Carriers with HLA-B Allele at Higher Risk for SCAR in Thai Population: Implications for Prevention of SCAR in Thailand and Southeast Asians

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HLA-B allele is clinically relevant genetic marker in pharmacogenomics, carrier status of at risk allele is useful information for avoidance of serious cutaneous adverse reactions, therefore the information of regional allelic distribution of *HLA-B* in Thailand is necessary for consideration processes for adoption of the genetic testing to avoid drug induced severe cutaneous adverse reaction (SCAR), including Steven Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN). This study reported the distribution of *HLA-B alleles* in 650 samples, which were randomly sampling from the 3rd Thailand national health examination survey (NHES) to represent population of 4 regional areas and a capital city, Bangkok.

The *HLA-B *15:02* allele, associated with Carbamazepine induced of SJS/TEN, was common with highest prevalence in Bangkok (10 %) and southern area (9.5 %). The frequencies of *HLA-B*15:02 allele* in central, northern, and northeast were at 7.33 %, 8.39 % and 9.25 % respectively. The *HLA-B*58:01*, associated with Allopurinol induced severe cutaneous adverse drug reactions (SCAR) was commonly identified in the northeast area (9 %) and Bangkok (9 %) but its frequencies were decreased in the northern (6.38 %), central (5 %) and southern area (4.5 %). In contrast, the *HLA-B*35:05* allele, associated with Nevirapine induced rash, was commonly identified in the southern area (4 %) and less common in the northeast (3.33 %), central (2.25 %), Bangkok (2 %) and northern area (0.67 %).

These results indicated that the distributions of *HLA-B alleles* are different in each region of Thailand, which may be depended from the pattern of ancestral migration. Since theThe distribution of *HLA-B alleles* from major geographic regions of Thailand are useful information for policy adoption of pharmacogenomics testing services in Thailand.

Abstract Code: P-115

Cutaneous Adverse Drug Reactions in Morocco: A Prospective Study

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Introduction: Cutaneous adverse reactions induced by drugs are common. They occur in 1–3 % of drugs users.
Aim: The aim of this study is to determine the frequency of cutaneous adverse drug reactions, describe the clinical aspects of these reactions and determine the scores of imputability relating the possible drug-effect relationship in Morocco.
Methods: This is a prospective study of cutaneous adverse drug reactions occurring in patients in El Idrissi hospital in Kenitra during the period April 2012-April 2013. The analysis of cause-effect relationships between the drug and the occurrence of clinical and paraclinical effects is conducted by the French causality assessment method with 7 scores from 0 to 6.
Results: Among 5137 hospital admissions, 45 patients developed 53 cutaneous adverse drug reactions, which was 1.02 %. The average age of the patients was 35.39 ± 0.53 years and the female-male ratio was 1.04 %. More than a fifth (22 %) of the patients showed toxidermia during their hospitalization and 11 % required a prolongation of their period of hospitalization. The beta-lactam antibiotics were responsible for adverse effects in 21.84 % of the cases, followed by the anti-tuberculosis drugs with 14.94 % of the cases. The most common types of cutaneous adverse reactions were urticaria (21.57 %) and skin eruptions (17.87 %). The French method of imputability gave the following results: 64.04 % of drug-effect relationships had an imputability score of I2, 15.79 % a score of I1, 14.91 % a score of I3, 3.51 % a score of I4 and 1.75 % a score of I0.
Conclusion: Cutaneous adverse drug reactions must be recognized in advance in order to ensure better surveillance and improve the safety of drugs.

Abstract Code: P-116

Lacosamide (Vimpat®), A Possible New Inducer of Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

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Introduction: Lacosamide is a novel antiepileptic drug (AED). AEDs are relatively frequently associated with severe cutaneous adverse drug reactions, including Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN); this is a leading cause of drug withdrawal.
SJS and TEN are rare but serious drug induced mucocutaneous disorders with systemic symptoms. SJS/TEN is characterized by massive epidermal necrosis, leading to high mortality and often long-lasting sequelae. The major distinctive feature in the spectrum of SJS/TEN is the total percentage of body surface area of detached or detachable skin, which in SJS is <10 %, in TEN > 30 %, while cases with 10–30 % involvement are classified as SJS/TEN-overlap.[1] Given the rarity of SJS/TEN (incidence estimated at 1.2–6/million inhabitants/year), the association is often only detected post-marketing.
Recently the first report concerning a probable lacosamide-induced SJS/TEN overlap was made in The Netherlands, suggesting an association between the drug and the event.
Case Report: A 73-year-old man was treated for post-operative persistent status epilepticus with lacosamide 100 mg/day, clobazam 10 mg/day and a bolus injection of 1000 mg phenytoin (earlier given without adverse reaction). Other drugs used were long-term hydrocortisone, valproic acid, and levothyroxine. Six days later an itching macular exanthema developed for which dexamethasone was given, while lacosamide was tapered over 8 days. Nevertheless the rash worsened, became burning and tender, also blistering and fever developed. Day 11 after onset SJS/TEN overlap was diagnosed; and confirmed by skin biopsy. After withdrawal of lacosamide, while clobazam was continued, the patient recovered on day 37 after reaction onset. Using the ALDEN-algorithm, a SJS/TEN-specific drug causality algorithm, the association with lacosamide was "possible", while all other drugs given were classified as "(very) unlikely".[2]
International Data at the WHO Uppsala Monitoring Centre: VigiBase® contains case reports of a further seven patients (likely duplicates excluded) with potentially lacosamide-associated SJS or TEN. We assessed the relationship-likelihood: "probable" in two, "possible" in three, "unlikely" in one and "unassessable" in another case. In one possible case we judged the event more likely to have been erythema multiforme.
Conclusion: The available information supports the hypothesis that lacosamide may elicit SJS/TEN. Further surveillance is needed.
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Abstract Code: P-117

Dipeptidyl peptidase-IV inhibitors and Bullous Pemphigoid in France: Analysis of Spontaneous Reports from French Regional Pharmacovigilance Centers and Manufacturers

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Introduction: Bullous pemphigoid (BP) is an autoimmune bullous dermatosis which is the most common blistering disease in old adult population in developed countries and could be, sometimes, drug induced. [1]

Three dipeptidyl peptidase-IV inhibitors (DPPI-IV), the "gliptins", as vildagliptin, sitagliptin and saxagliptin (monotherapy and associated with metformine) are marketed in France between march 2008 and november 2012 and widely used as antihyperglycemic drugs in patients with type 2 diabetes mellitus. Occurrence of PB with patients treated by DPPI-IV has already been reported in few cases reports but remains underdiagnosed and under-reported[2]

Aim: To explore associations between BP and vildagliptin, saxagliptin and sitagliptin since their marketing authorization in France.

Methods: We collected all spontaneous reports of BP to vildagliptin, sitagliptin and saxagliptin received by the French Regional Pharmacovigilance Centres and by the 3 manufacturers of DPPI-IV since the beginning of marketing in France of these agents to 7th October 2013. For each spontaneous report involving DPPI-IV, information about patient (age, gender, medical history) and characteristics of BP were collected.

Results: A total of 38 cases of BP with vildagliptin (26 cases), sitagliptin (11 cases) and saxagliptin (1 case) were collected. Patients were mostly males (61 %) with a mean age of 71.9 years. Among patients with a medical history, 60 % of them had a hypertension. Delay of occurrence of the BP varied from 10 to 730 days with an average of 306 days. In more than 50 % of cases, recovery occurs within one month which strongly suggests the involvement of drug.

Conclusion: The occurrence of BP during DPPI-IV treatment prompts physicians to carefully monitor the occurrence of epidermal blisters during all the treatment because the onset could be late (until 2 years) and highlights the importance of relevant and early explorations to avoid drug involvement. The withdrawal of the drug leads mostly to a resolution of symptoms.

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Abstract Code: P-118

Surveillance in Medical Records and Claims—State of the Art and Future Developments

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The capability for secondary analysis of electronic medical records and transactional insurance claims databases for epidemiological studies has existed for many decades. As the number of such electronic data repositories has increased, we have seen greater and greater numbers of studies to ensure the safety of medicinal products through formal hypothesis testing. As such databases have very different and often unique strengths and weaknesses, the ready linking of such data has led to more interest in conducting analysis across networks of many distinct databases, and with this increased ease of access there is heightened interest in determining their use for near-real time surveillance. However, there remains a limited body of research on such linkage through standardized data structure influences analyses, and differences between different data standardization approaches. Also while these databases are rich there are on occasion missing information of crucial importance for Pharmacovigilance. Increasingly, therefore, there are efforts to better enrich the existing data by nesting primary data collection and also to mine the narratives and other information not captured in the structured data.

Results illustrating developments against these challenges will be presented. Specifically we describe the use of a Natural Language Processing (NLP) approach to extract clinical concepts from narratives on the US EMR data set called Humedica focussing on acute liver injury identification in an Irritable Bowel Disease (IBD) population. We also present results showing comparison of different widely used (Mini-Sentinel and OMOP) approaches to standardization of database structures, focussed on analysis of the Humana US insurance claims database. Developing and linking data is very much an international development, we describe efforts are underway to actively consider the value of Common Data Models in China in facilitating this process. In the future we anticipate even more widespread development, linking and analysis of electronic data sources, and ever more effective leverage of such data; often across very different sources. We expect more widespread appreciation of the value of secondary analysis of existing Electronic Medical Record data whether for studies or surveillance activities, and better acceptance of the circumstances under which a primary data collection study, whether interventional or not, is a more appropriate analysis approach. Lastly we also anticipate more frequent nesting of primary data collection for Pharmacovigilance in existing healthcare data sets to produce enriched data sets for analysis.

Author Index