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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

ABSTRACTS

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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

The International Society of Pharmacovigilance (ISoP) is devoted to developing its activities on a worldwide basis towards supporting safer use of medicines in clinical practice.

ISoP aims to promote the use of all types of information and methodologies in providing optimal drug treatment for patients. The Society is not only for clinical pharmacologists, pharmaceutical industry representatives, epidemiologists and regulators, but also for practising clinicians, other healthcare professionals and anyone else who is interested in learning about better ways for patients to receive and use medicines safely.

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From Argentina to Vietnam, from countries in South-America to North-America, from Europe to Asia and Australia via Africa, we have members in all five continents.

"By becoming a member of ISoP, you will have the opportunity to share your knowledge and ideas and to contribute to improving pharmacovigilance activities worldwide".
Hervé Le Louet, President of the International Society of Pharmacovigilance

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Opening Lecture

O 01

Patient Safety Today—From Identifying Problems to Implementing Solutions

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In the last 2 decades, patient safety and quality improvement within healthcare have emerged as solid areas of scientific endeavour, as well as key areas of focus for clinical practice and for health policy-making—including interventions delivered at national and even international level.

In this lecture I will describe the evolution in the field of patient safety—from early risk management perspectives to more proactive quality improvement approaches and patient involvement currently reported in the scientific literature and implemented in clinical practice. I will cover the emergence of patient safety incident reporting across healthcare specialties; draw some parallels between it and pharmacovigilance methods; and describe an emerging philosophy driving the development and utilisation of incident reporting systems in healthcare.

I will finally provide an overview of implementation elements of safety and quality improvement, including aspects of behavioural change, organisational readiness to change, and contextual factors that impact on practical application of improvement strategies.

Keynote Lecture 1

O 02

The Future of Pharmacovigilance

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Pharmacovigilance has seen major change over the last 10-years. This change has included:

- Broadening of scope to include adverse reactions with off-label use, misuse and abuse
- Greater proactivity of interventions through risk management planning, greater use of studies to supplement spontaneous reporting of suspected drug reactions, and investment in accessibility to data from electronic health records and insurance claims
- Replacement on interval safety reviews ta move to cumulative benefit risk reviews through the Periodic Benefit Risk Evaluation Report
- Faster and more inclusive regulatory assessment and decision-making through formalisation of signal evaluations and referrals
- Patient engagement through reporting, through committee membership and through major increases in transparency
- Application of a quality systems approach with routine audit and inspection.

This lecture will look to the next 10-years and consider which of the changes already implemented will have the greatest impact and will explore which opportunities on the horizon are likely to be realised. This will include:

- Further advances in regulatory sciences relevant to pharmacovigilance (statistical approaches to signal detection, pharmacoepidemiological methods, decision-making methods, impact measurement in pharmacovigilance etc.)
- How to overcome the operational barriers to accessing large European health care datasets
- Personalised medicines becoming a reality
- Realising the potential of big data to support surveillance and decision-making and the role of social media for distributing risk minimisation messages and for surveillance
- Decision-support at the individual patient level

The lecture will conclude by identifying the key enablers that are needed for the benefits promised by these enablers to be realised.

Parallel Session A—Risk Management in Pharmacotherapy

O 04

Medication Errors—EU Regulatory Initiatives on Risk Minimisation and Error Prevention

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Introduction: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Medication errors are the most common preventable cause of adverse events in medication practice and present a major public health burden.

Aim: This session will show how reducing errors in prescribing, dispensing, preparing or administering authorised medicines is increasingly dealt with in the EU as a shared responsibility between patients, healthcare professionals, regulators and pharmaceutical industry at all levels of healthcare delivery.

Methods: Draft guidance on medication errors was released for public consultation in April 2015 to support pharmaceutical industry and regulators in the implementation of the changes introduced with the EU pharmacovigilance legislation. These changes included a modification of the definition of an "adverse reaction" to explicitly include events associated with medication errors, and the requirement for national competent authorities responsible for pharmacovigilance in EU Member States to collaborate and exchange information on medication errors resulting in harm with patient safety organisations.

Results: Taking into account the comments of the public consultation, guidance is provided on how to record, code, report and assess medication errors associated with adverse reactions for EU pharmacovigilance purposes, including recommendations to marketing authorisation holders on how to report information on medication errors which are brought to their attention but have not caused adverse reactions. This information is required in periodic safety update reports and in risk management plans to

allow regulators to continuously evaluate the benefits and risks of a medicine based on real life data.
The good practice guidance also provides an overview of risk minimisation and prevention strategies for medication errors based on past-experience of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The main sources and types of medication errors will be discussed, including proposals for measures to minimise the risk of medication errors throughout the life cycle of a medicine. As product-specific addendum of this guidance a risk minimisation strategy for medication errors with novel high strength insulin products (i.e. higher than EU-wide standard 100 units/ml concentration) and fixed combination insulin products has been developed.
Conclusion: The release of the final guidance end of 2015 will support the implementation of the new legal provisions by all stakeholders involved in the reporting, evaluation and prevention of medication errors for the benefit of patients and public health.

O 05

WHO Guideline: Reporting and Learning Systems for Medication Errors: The Role of Pharmacovigilance Centres

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Over the years, Pharmacovigilance centres (PVCs) have been involved in Medication Errors (ME) and preventability of adverse drug reactions (ADRs).
Following the Institute of Medicine's report results in 1999, the patient safety concept increased to a high level of health care priority. Thereafter, the World Alliance for patient safety was launched in 2004 after collaboration and discussion with the WHO Programme for International Drug Monitoring and the Uppsala Monitoring Center (UMC), the issue of ME being one of its main interests.
Following that, a WHO/UMC Project funded by the World Alliance for Patient Safety and leaded by the Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM) has been launched for 2006–2007 to extend the role for PVCs to include collection of information on adverse incidences related to ME and to enable international analysis of these data and to disseminate findings internationally.
The results raised the need to coordinate efforts between countries to optimize ME detection, and its analysis and to build bridges linking PVCs, Poison Control Centres and Patient Safety organizations in order to avoid duplication of workload.
To this end, in 2009, the monitoring Medicines Project, leaded by WHO and UMC was launched. One of its coordination objectives leaded by the CAPM divided in two work packages (5 and 6) was to expand the role and scope of national pharmacovigilance centres to prevent medicine-related adverse events with the outcome to put in place a preventability method "P Method", to standardize common terminology used by PVCs and Patient safety Organizations, to optimize ME detection through Individual Case Safety Reporting (ICSRs) form and to outline education material developed for raising awareness of Health Care Professionals about preventable ADRs.
The work package 6 was dedicated to draft and edit a WHO guideline1 entitled: Reporting and learning systems for Medication Errors: the role of Pharmacovigilance centres, to increase the capacity of national pharmacovigilance centres to identify and analyse preventable ME and to stimulate cooperation between national pharmacovigilance centres and the World Alliance for Patient Safety.
The aim of our work is to present the WHO guideline which is intended to PVCs, medication safety organizations and patient safety organizations focusing on the role of PVCs in raising awareness, improving existing ICSRs, using specific tools to identify risk contributing factors, putting in place Risk Minimisation Actions and outlining the importance of collaborations between stakeholders.
Further sources of information/Reference

1. WHO guideline: Reporting and learning systems for medication errors: the role of pharmacovigilance centres.

O 06

Patient Adherence and Patient Safety

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Medication adherence has gained wide recognition as a central element in the optimization of ambulatory medical care. The predominant form of variable adherence is under-dosing, resulting from (a) missed doses during implementation of the prescribed dosing regimen, (b) non-initiation of dosing, or (c) early, complete discontinuation of dosing. Variable adherence can also take the form of over-dosing when dosing intervals are too short or when more than the prescribed number of doses are taken. The latter happens typically when the patient does not remember if a dose is taken and, in doubt, takes an extra one. Depending on the drugs' pharmacological properties, under-or over-dosing can result in lack of effectiveness and/or safety issues. The problem of safety is more important when its relation to exposure is steep, for example, with anticoagulation treatments. In practice, when precise implementation of a dosing regimen is required, it becomes critical to provide patients not only the drug but also a monitoring system that supports the management of adherence to medications.
A more profound consequence of medication non-adherence arises when the dosing regimen has been based on results of adherence un-informed clinical trials. Currently, in drug development, the focus lies primarily on maximizing efficacy and thus the evaluation of doses near the maximum tolerated dose. From the use of reliably-measured adherence in clinical trials, e.g., electronic monitoring, it has been shown that non-adherence is widely prevalent not only in medical practice but in drug trials as well. Thus, when reliable adherence measurement methods are not in place, clinical trials provide an underestimation of the drug's safety profile. This adherence-uninformed approach results often in inadequate dose finding with a clear trend towards doses that are higher than needed. The consequences of overestimated dosing requirements are increased incidences of side effects that often lead to treatment discontinuation and thus short persistence to treatments. In drug development, adherence-informed

clinical trials, based on reliably precise measurement of adherence, will yield more informative data on both safety and the dose-dependence of efficacy, resulting in better patient satisfaction and longer persistence with treatment.

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O 07

Evaluating Prescriber Concordance with Prescribing: Results from a Post-Marketing Study in Primary Care Setting

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Introduction: At launch (2005), ivabradine (Procoralan©) was indicated for treatment of chronic stable angina pectoris in patients with normal sinus rhythm, with a contraindication and/or intolerance for beta-blockers. A drug utilisation study was conducted to support risk management of the drug. Study objectives included examining contraindications, warnings for use and incidence of two adverse events: visual phosphenes and bradycardia (persistent heart rate <50 bpm).

Aim: To develop a tool for use to support assessment of prescribing discordance with prescribing recommendations and explore impact on phosphenes and bradycardia incidence.

Methods: An observational single exposure cohort study. Exposure data were collected from dispensed prescriptions issued by primary care physicians November 2005 and May 2009; outcome data (including pre-existing patient medical conditions and/or drugs which carried contraindications and/or warnings for use) from forms sent to physicians ≥6 months after each patient's first prescription. An algorithm based prescribing framework was developed and assisted with the assessment of available information according to the contraindications and warnings for use in the Summary of Product Characteristics. To explore impact of prescriber discordance, risk [%; +95 % confidence interval (CI)] of phosphenes and bradycardia were calculated by framework group (≥1 contraindication; ≥1 warnings for use; combination of >1 contraindication/>1 warning for use; concordant; unknown). Descriptive statistics were also calculated.

Results: Final cohort comprised 4624 patients, median age 68 years (IQR 60, 77); 57 % (n = 2663) male. Contraindications and warnings for use were assessed for 3357 patients: 74 % (n = 2491) were concordant, 21 % (n = 701) had warnings for use, 4 % (n = 124) had contraindications and 1 % (n = 41) had a combination of contraindications and warnings for use. Bradycardia was reported for 96 patients (2.1 % [1.6, 2.5] cohort) of which 73 were assessed by framework group: n = 4 (3.2 % [0.9, 8.3]) were contraindicated, n = 17 (2.4 % [1.4, 3.9]) had warnings for use, n = 1 had combination of both, and n = 51 (2.0 % [1.5, 2.7]) were concordant. Phosphenes were reported for 140 patients (3.0 % [2.5, 3.6] cohort), of which 104 were assessed by framework group: n = 2 (1.6 % [0.2, 5.8]) were contraindicated, n = 23 had warnings for use (3.3 % [2.1, 4.9]), n = 1 had a combination of both, and n = 78 (3.1 % [2.5, 3.9]) were concordant.

Conclusions: In this study, the incidence of bradycardia and phosphenes was common in all concordance groups, although estimates lacked precision. This study demonstrates the feasibility of using a framework to assess prescribing discordance as reported in drug utilisation studies to identify at-risk populations, which may help support post-marketing risk: benefit evaluations.

O 08

Medication Errors Detected Among the Spontaneously Reported Adverse Drug Reactions to the Croatian Agency for Medicinal Products and Medical Devices

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Background: Medication errors are the most common preventable cause of adverse drug reactions (ADRs) in medication practice and present a major public health burden.

Aim of the study: The objective of the study was to identify, evaluate and describe medication errors (ME) among the spontaneously reported ADRs to the Croatian Agency for Medicinal Products and Medical Devices (HALMED).

Method: A retrospective observational study was performed on 100 spontaneously reported ADRs in 2013. The previously validated "P-method"1 was employed to systematically detect MEs in individual case safety reports (ICSR) sent to the Croatian pharmacovigilance centre (PVC) at HALMED. ME that lead to ADR identified by reporter as well as ME suspected by assessor are described.

Results: Ninety-seven MEs were detected in 100 analysed cases [gender 38 M, 62 F; age 56.1 ± 21.9 (range 2–93); number of medicines 2.8 ± 2,0 (range 1–13), comorbidities 1.7 ± 1.2 (range 0–5)]: 21,65 % (n = 21) related to a suspected drug led to an ADR, whereas 78,3 % (n = 76) related to both suspected drug or concomitant therapy did not lead to harm. In only 3 cases (14, 29 %) ME that lead to ADR was identified by reporter. Out of 36 (36 %) spontaneously reported serious ADRs, 9 (25 %) were caused by medication errors. The most commonly identified preventability criteria for ADR occurrence was "Drug–drug interaction" reported in 24.7 % of overall MEs, followed by "Incorrect dose" (21.6 %).

Conclusion: A high proportion of MEs was identified in ICSRs sent to PVC with one fourth of the serious ADRs caused by medication errors. In 20 % of reported ADRs MEs was identified. In most cases (86 %), ME was suspected only by assessor. In process of identifying a medication error in practice it is very hard to check that in particular case it was unintended failure in the drug treatment process. Process of identifying ME is very sensitive and relationship between reporter and national pharmacovigilance centre as well as legal implications in the context of HCP liability in some countries must be taken into account. Our results indicate the need to capture suspected ME by assessor in databases as well as promoting reporting of ME and customizing ADR forms for reporting ME.

Parallel Session B—Vaccines

O 09

Methodologies for Vaccine Safety Surveillance

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Introduction: Vaccine safety surveillance post marketing can be considered as having three main components. Firstly it is necessary to rapidly identify signals of possible safety concerns through vaccine—pharmacovigilance, signals then need a quick initial evaluation to determine whether they are of sufficient concern for further action which then may lead to special studies to further assess the possible association.
Aim: To compare epidemiological methods used to assess vaccine safety signals.
Methods: Methods have developed over recent years and include case–control and cohort designs as well as the self-controlled case series (SCCS) method and the case-coverage method. The methods are presented and compared using vaccine safety questions that have arisen over the past 20 years, including MMR-autism, influenza vaccination-Guillain Barre syndrome, influenza vaccination-asthma, rotavirus vaccine-intussusception and pandemic influenza vaccine-narcolepsy.
Results: These examples demonstrate clear advantages of the SCCS when assessing events where any increased risk would be in a relatively short period after vaccination and where confounding is likely to be present for other designs. Where onset of the event is less clear and any risk likely to be over a longer period other designs may be preferable.
Conclusion: With increased availability of large linked datasets, evaluation of safety signals using SCCS and other designs should be possible in an increasing number of countries.

O 11

Monitoring Adverse Events Following Influenza Vaccination in General Practice: Evaluation of Different Methods to Increase the Inclusion Rate of Patients

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(1) Netherlands Pharmacovigilance Centre Lareb, Lareb Intensive Monitoring, 's-Hertogenbosch, The Netherlands

Introduction: The Netherlands have developed a web-based active monitoring system where patients, vaccinated with influenza vaccine, can report the occurrence of adverse events. Patients are vaccinated in general practice and general practitioners (GP's) invite their patients to participate in the monitoring study. In this study we focused on informing the GP's and to support them in inviting their patients. The objective was to evaluate whether conventional compared to new methods of support made towards the general practitioners resulted in higher inclusion rates (IR) of patients.
Methods: 85 participating GP's were divided into three groups: one group of 60 GP's received only study material: flyers about the study to distribute to patients and a letter with instructions (conventional method). The instructions included: give each patient a flyer and a short explanation. 15 GP's received the study material and were subsequently called by the researchers to ask whether the information was clear. 10 GP's were visited by a researcher: the study material was handed over with an explanation. An evaluation questionnaire was sent to GP's to ask their experiences of the process of inviting patients.
Results: Of the participating GP's 75,945 patients were eligible for vaccination. 1401 patients participated in the web-based monitoring. The inclusion rate of patients of the conventional group was 1.65 %, and the IR for the called and visited group was respectively 2.61 and 2.24 %.
The response rates for the questionnaire were 73.6 for the conventional group, and 46.7 and 60.0 respectively for the called and visited group. The GP's of the visited group handed over all flyers. In the conventional group and called group the GP's gave the flyers in 77.8 and 28.6 % of the cases. In the other cases the flyers were presented on a pile in the waiting room. In the conventional, called and visited group the IR were highest respectively 2.26, 2.90 and 2.28 % when the GP's actively handed over the flyer. When flyers were presented on a pile the IR of the conventional method and called group was respectively 1.08 and 2.03 %.
Conclusion: The highest IR was seen in the group of GP's who were called. In addition the IR was the highest when patients were given a flyer. This study showed evidence that more efforts towards GP's by a phone call or visit increases the IR compared to the conventional method. Additionally, more efforts of GP's towards informing patients also increases the IR.

O 12

Identification of Vaccine Safety Signals in VigiBase

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Introduction: The WHO Global Individual Case Safety Report database, VigiBase®, contains over 10 million reports, of which approximately 10 % concern vaccines. In the last 10 years, only 1 % of the signals communicated by the Uppsala Monitoring Centre related to vaccines, raising uncertainty as to the adequacy of current methodology to detect vaccine signals in VigiBase.
Aim: To explore if VigiBase could serve as a source to detect vaccine signals.
Methods: A list of vaccine-AE (WHO–ART preferred terms) pairs, based on reports with at least one of six focus vaccines reported as suspected, was constructed. The focus vaccines were meningococcal, pneumococcal, varicella zoster, rotavirus, and human papilloma virus (HPV) vaccines, selected given their relatively recent or currently debated introduction into childhood vaccination programmes. The list was limited to serious events, defined as WHO–ART critical terms or as events for which at least 90 % of the reports were classified as serious. Vaccine–AE pairs with more than 30 reports and those reporting common vaccine events (e.g. injection site reaction, fever) were excluded from the list. Remaining pairs were prioritized using vigiRank [1]. The disproportionality component of vigiRank was calculated with a background restricted to vaccine reports (ATC code J07) and was complemented with an unmasking strategy [2].
Results: Out of 889 vaccine–AE pairs, 101 were clinically assessed. The majority of the assessed pairs reported rotavirus, pneumococcal or HPV vaccines (about 30 % each). The WHO–ART System Organ Classes with the most assessed pairs were Neurological disorders (11 %),

Gastrointestinal disorders (10 %), and Vascular, bleeding and clotting disorders (10 %). Of the 101 assessed vaccine–AE pairs, 20 % were considered known, 57 % were assessed as non-signals, 11 % were to be kept under review, and 12 % needed further case series assessment to determine whether a possible causal relationship exists. Four of the pairs needing further assessment related to HPV vaccines, three to pneumococcal and meningococcal vaccines each, and two to varicella zoster vaccines.

Conclusion: This adaptation of routine signal detection methodology uncovered potential signals related to vaccines and confirmed that VigiBase can serve as a valuable source of information on vaccine safety.

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O 13

Asymptomatic Immunization Errors Reporting in Morocco

A. Tebaa[1], S. Belamalem[2], L. Alj[1], R. Benkirane[1], R. Soulaymani-Bencheikh[1]

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Introduction: Medication errors do occur with both drugs and vaccines and they are more frequent with drugs where the focus is on the problem look or sound-alike names. There are enormous numbers of vaccination errors that take place, some unfathomable. Vaccine Administration Errors are preventable events that could lead to reduced vaccine effectiveness.

Aim of this study: To describe the profile d 'immunization errors reported in CAPM in order to review the types of errors administration, to identify common problems and to implement potential solutions.

Methods: All immunization errors recorded by CAPM were retrospectively analysed during the period 2009 to 2013. In our study were included all errors related with vaccines that occurred without events.

Results: Of 853 medication errors recorded in Pharmacovigilance database, 32 were related to asymptomatic immunization errors with an average of 4.2 ± 0.8 per year for all AEFI reported. The errors occurred with the routine immunization in 79 %, in mass campaign in 21 %. The male was the most represented with a frequency of 59 % ($\chi^2 = 0.5$, $P > 0.05$). The infants were involved in 72.2 % of errors. The most incriminated vaccines in these immunization errors were: anti-Rubella–Measles vaccine in 20 %, Anti pneumococcal vaccine and Measles vaccine in 15 % each. The common types of errors were the Wrong dosage in 37 %, Wrong vaccine (25 %), Wrong route/site (15 %), Wrong time (10 %), Wrong patient (8 %) and Expired vaccine (5 %).

Conclusion: Immunization errors are preventable and detract from the overall benefit of the immunization program. The identification and correction of these incorrect immunization practices are of great importance. Providers need to be aware of the system and willing to self-report. Public and private partnerships are an effective way to address knowledge gaps and implement timely solutions.

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Parallel Session C—Risks and Benefits of Medicines for Women

O 14

Medicines for Women: Medicines for Half the World

M. Harrison-Woolrych[1,2]

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Medicines for women are not a minority issue. Women take more medicines than men and during their reproductive years take primary responsibility for contraception in most relationships. As mothers, women are also responsible for administering medicines to babies (in utero and after delivery) and to children too. Another role of many women as carers extends their responsibilities and the health of women determines the well-being of communities worldwide.

In this lecture, I will give a broad overview of key issues relating to medicines for women, focussing on clinical pharmacovigilance perspectives. These will be considered in three broad areas as presented in the recently published book Medicines for Women [1]:

1. How should we prescribe medicines for women?
   Health professionals providing information to women about medicines and other treatment options should consider some specific questions before a prescription is given. These will be discussed and reference will be made to special populations, including pregnant and lactating women.
2. Benefits and risks of specific medicinal products for women
   Certain medicines, devices and vaccines are used exclusively by women and others have predominantly female utilization. An overview and some interesting facts will be presented. Recently published evidence on specific medicines adds to ongoing benefit–risk assessments.
3. International perspectives and risk communication
   The role of ISoP in discussing international perspectives in pharmacovigilance is especially important in the area of medicines for women's health. In many countries, gender inequality and poverty means women are vulnerable and face challenges maintaining their health.

Global collaboration and communication is essential in monitoring the safety of women's medicines. We will briefly discuss how women may access high quality information about the risks and benefits of their medicines.
In conclusion, some recommendations for the future will be presented. These include involving women in discussions and decisions about their medicines and having a holistic approach which values women and considers their socio-cultural environment in all stages of regulation, monitoring and prescribing medicines.

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O 15

Evidence-Based Use of Menopausal Hormone Therapy

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Despite reductions in use in many higher income countries in the early 2000s, menopausal hormone therapy (MHT) remains a commonly used medication. It is an effective treatment for menopausal symptoms and reduces the risk of fracture. However, use results in a net increase in the risk of certain potentially life-threatening conditions including breast cancer, stroke, ovarian cancer and venous thromboembolism, and use of oestrogen-only MHT increases the risk of endometrial cancer in women with a uterus. Overall risks increase with increasing duration of use and with age and are greater for oestrogen-progestagen MHT than for oestrogen-only MHT.
There is agreement between key drug regulatory authorities that MHT use should be targeted for moderate to severe menopausal symptoms, and not for the prevention of disease. Strategies for minimising MHT-associated risks include the following: Using MHT for the short term treatment of menopausal symptoms (e.g. hot flushes, night sweats, vaginal dryness) only; women considering use of MHT should be informed of its risks and benefits; MHT should not be used for the prevention of disease, or (e.g. in Europe and Australia) as first line treatment for osteoporosis; MHT should be used for as short a period of time as possible and the need for continuing use should be reviewed 6-monthly or annually. Preferential use of oestrogen-only MHT and transdermal oestrogen-only MHT, including in women with a uterus, are also likely to reduce certain MHT-associated risks, compared to use of oestrogen-progestagen MHT and oral MHT.

O 16

Safety of Medicines During Breastfeeding

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Risks of a medicine for the infant should be questioned when pharmacotherapy is necessary for a breastfeeding woman. Most medicines enter breast milk in some amount and possibly could have an impact on the infant. However the possible risk should always be weighed against huge benefits of breastfeeding. Breast milk is not only the optimal nutrition for the infant, it provides also an important immune protection and series of further benefits for both mother and child. The premature termination of breastfeeding is an important handicap for both, therefore careful assessment of breastfeeding benefits and possible risk of adverse drug reactions in the infant should be done.
When assessing possible risk of a medicine in breast milk for the infant 4 basic aspects should be taken into consideration—what is the "dose" of a medicine an infant takes with breast milk, how acts pharmacokinetics in the infant, what do we know about safety profile of the medicine and about adverse reactions in breastfed children and what is the age and state of health of the infant.
The optimal choice of a medicine for a breastfeeding woman is a medicine with a very low penetration into breast milk (very low calculated relative infant dose), a short elimination half-life (no accumulation in the infant anticipated), good experience with the treatment during breastfeeding and relatively low-risk safety profile.
There are rather few medicines which are so risky that breastfeeding should be contraindicated. Most medicines could be used during breastfeeding under very careful supervision of both mother and physician. If an adverse reaction appears in the infant it develops gradually and measures can be taken in time. In some cases the adequate regimen of drug intake and breastfeeding could be established, in other cases some specific health tests or drug monitoring could be useful. The close collaboration between mother and physician is of major importance.
When deciding about the medicine for a breastfeeding mother most information possible should be sought. The basic information can be found in the Summary of Product Information of each medicinal product. This information agreed in drug regulatory process should be amended by current scientific knowledge. A good source of information is in the database LactMed with free access on http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT.

O 17

A Woman is Not Like a Man: Why Risk Communication for Women is a Whole New Game

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Note: This abstract is a summary of material taken from Chapters 18 and 19 of Medicines for Women and forms one part of the presentation of key aspects of the book's content. It does not, therefore, follow strictly the content guidelines for research abstracts. References have not been included because of the word-limit constraint.
Introduction: Women across the world are disadvantaged in healthcare in a number of ways. Inferior treatment for heart disease and the neglect of menopause as an area of research are two examples. Drug information, and risk communication in particular, have rarely been tailored to the specific needs and preferences of women.
Aim: To highlight some of the unique and neglected aspects of women's lives and experience of healthcare that point the way to more effective risk communication for women.

Overview of content: Risk communication for women must take into account the multiple cultural, social, psychological and risk variables which impact their lives. These include their preferences for provider sex, sources of information and decision-making style; the degree of self-determination in their cultural setting and the level of subjection to male behaviour and expectations (including health professionals); their exposure to abuse and unwanted pregnancies; their unique and diverse attitudes to motherhood, contraception, menopause, body-image, and much more. Across cultures these all vary enormously and no one model or profile can be adduced.

Young women face a particular series of risks in their lives that profoundly affect their health (alcohol, unprotected sex, eating disorders, depression and suicidality, for example). Many of these are not disclosed to health professionals and therefore become a dimension of hidden risk that is not accounted for in diagnosis, risk communication and treatment.

Specific challenges in risk communication for women, amongst many others, arise in the cases of HPV vaccination, HRT, epilepsy in pregnancy and contraception.

Effective risk communication is a critical element in ethical therapeutic relationships that respect the autonomy and unique characteristics of individual patients. Risk communication for women is a major sub-set of the discipline in general, and one that requires radical reappraisal and reformed practice.

Parallel Session D—Benefit/Burden of Pharmacovigilance

O 18

Pharmacovigilance and Pharmacoeconomics: The Burden of Pharmacovigilance on the Health System, Rheumatoid Arthritis as an Example

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Introduction: A health system consists of the resources, actors and institutions whose primary intent is to improve or maintain health. Appropriate use of medication is thus necessary, although a medication may cause harm. Especially, the major problem that confronts primary care health professionals on a daily basis, is the risk of adverse drug reactions. It is noteworthy that 5 % of all patients suffer an adverse drug reaction and constitute the common cause of hospital admission. Biotechnological medicines have improved the treatment of various diseases and the quality of life of patients, but they may lead to adverse events. These events affect disease progression and health expenditures. Rheumatoid Arthritis (R.A.) is an autoimmune disease for which biotechnological medicines are prescribed. RA has serious economic impact. Especially, the annual cost of RA is 41 billion euros in the U.S.A. and 45 billion euros in Europe, which are increasing dramatically with appearance of an adverse event.

Aims: To record the ADR of biotechnological drugs prescribed for R.A., to assess their possible effects on both patient and health system and to develop a tool aiming the efficient use of biological medicines.

Methodology: A review of existing literature on adverse events of biotechnological medicines for RA and analysis of all available data from Eudravigilance were conducted. The collection of adverse events data from rheumatology clinics of various hospitals will be conducted. Finally, any algorithm/tool currently utilized to guide the selection of the most appropriate treatment will be assessed.

Results: 60 % of patients are female aged 18–65 years. 20 % of reports indicated that an infection has occurred, 15 % highlighted the existence of inflammation at the site of injection and 12.5 % reported a gastrointestinal disorder. The occurrence of musculoskeletal problems, hyperplasia and nervous disorder estimated at 10 % of the reports and the respiratory problems approximately 8 %.

Conclusion: Infection or inflammation at the site of injection is the most common adverse events altering microbiological profile of patient. A possible relationships/associations between certain parameters (for example genome and the appearance of an adverse event) which will contribute to the safer and efficient use of biological drugs will be examined. In addition, the total average medical costs were reported to range from 5720$ to 5822$, while the average number of days absent from work due to a person's RA was reported to range from 2.7 to 30 days/years. The appearance of adverse events increases dramatically the therapeutic costs.

O 19

Another Perspective in Pharmacovigilance

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Introduction: Since the early 60's voluntary reporting is an important tool to study the safety of drugs after their introduction on the market. For signal detection purposes, there is an increasing involvement of other approaches like observational studies. One of the prominent goals of our efforts is to signal hitherto unknown adverse drug reactions (ADRs) and finally to establish their incidence. From a regulatory perspective this information is needed to enable a continuous evaluation of the risk/benefit balance. From a clinical perspective however, detection and validation of signals is merely the starting point of gathering knowledge that is actually needed to treat our patients, so we need to focus on other aspects associated with the occurrence of ADRs as well.

The way and circumstances in which drugs are used, may influence the type and course of ADRs. In addition information on clinical presentation, time to onset, duration, severity and impact on the quality of life of the ADRs is often not readily available for healthcare professionals and patients. However, for a proper understanding of the impact of ADRs for our patients, this information is needed. For this reason, monitoring the safety of drugs should not be limited to establishing the causal relationship between drug and ADR only. A shift toward the perspective of patient, physician or pharmacist is needed to provide information that is valuable for both regulator as well as healthcare professional and patient.

Aim: In this lecture the need to study the aforementioned aspects of ADRs from the perspective of patient and physician will be discussed. Examples will be given of the way in which the presentation of ADRs may differ from the information mentioned in the product information. Finally possible approaches will be highlighted that enable studying these aspects of ADRs in daily circumstances in more detail.

O 20

An Assessment of Utility and Burden Associated with the Vandetanib (CAPRELSA®) Restricted Distribution Program in Canada

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Introduction: Vandetanib (CAPRELSA®), approved in 2012 in Canada, is indicated for the treatment of advanced medullary thyroid cancer. QT-prolongation or torsade de pointes is considered in the risk management plan as an identified risk. To minimize this risk a restricted distribution program (RDP) has been implemented. Although shown effective, there are limited data on its associated burden to patients, health care professionals and the healthcare system.
Aim: To assess the utility and burden associated with the different components of the vandetanib RDP.
Methods: A mixed method evaluation is being used to address both the qualitative and quantitative aspects of burden. Target populations include medullary thyroid cancer patients as well as healthcare providers (prescribers, nurses, and pharmacists) who are certified/registered (i.e. exposed) to the vandetanib RDP. Unexposed patients and healthcare professionals are those who did not go through the certification process for the RDP and are therefore receiving/prescribing standard oncology care. For each population, a mapping of patient journeys through the healthcare system is conducted with an economic evaluation according to a third-party payers perspective.
Results: Major components of the vandetanib RDP will be presented and areas of redundancies between the RDP and standard oncology care consisting mainly of hospital protocols will be identified. For each component, the qualitative burden for HCPs and ultimately patients will be detailed along with their associated costs using third-party payers perspectives.
Conclusions: Assessing the burden of risk minimization measures should be systematic in order to avoid duplication of efforts and optimize the effectiveness of risk management plans.

O 21

Building Up a Signal Management Framework For a Resource-Limited Health Authority

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Introduction: Pharmacovigilance is about safety signals management throughout the medical product lifecycle. However, managing numerous signals from various sources becomes big challenges in Taiwan as well as other resource-limited countries.
Aim: To develop a prioritized yet comprehensive signal management scheme that incorporates all pharmacovigilance activities in needs.
Methods: To address diverse needs of the health authorities, a prioritization principle of drug safety signals was constructed. Issues that might affect our decision of prioritizing safety information will be categorized and weighted accordingly.
Results: ADR reporting system, drug injury relief system, and global drug safety news were incorporated as mass pool of signals. Signals then were prioritized by 5 domains (Intensity of Signal, known knowledge, Possibility to study in NHIDB, degree of impact, and others) which are further categorized by total of 17 subjects (subdomains). A radar plot will be generated automatically to check the magnitude of each signal. Filtered signals will then be followed by signal refinement procedure by performing case series review, literature review, and claim database drug utilization studies. If the result obtained deserves further actions, complete pharmacoepidemiology studies will be implemented for signal evaluation. Since this framework has been employed in May 2014, 25 ADR case series analysis, 5 prescription pattern analysis, and 4 pharmacoepidemiologic studies have been carried out last year.
Conclusions: This signal management procedure incorporated both passive and active pharmacovigilance schemes. Continuous signal life cycle concept is also addressed. This framework is aimed to guide the health authorities dealing with mass signals effectively based on limited resources. The end results can be used for development of national risk communication and management plans.

Parallel Session E—The Roles of PV Centers and Community Involvement

O 22

Patient Involvement for a Better PV Knowledge

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Patient reporting of adverse drug reactions (ADRs) has existed in several countries for decades, but throughout Europe the role of patients as a source of information on ADRs has not been fully accepted until recently. Studies have established the significant contribution of patient reporting to ADR signal detection.. Examples of signals where consumer reports have been of crucial importance for signal detection in the Netherlands are persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors and aggression in relation to SSRIs. . Information from patient reports gives their perspective on ADRs and their views may change the way the benefit–harm balance of drugs is perceived and assessed today, and, being the ultimate users of drugs, consumers could have a relevant influence in the regulatory decision-making processes for drugs.
With inviting patients as reporters to spontaneous reporting systems, pharmacovigilance has new possibilities to share its knowledge with the end users of drugs, namely the patient. To achieve this it is important to raise the public awareness of ADR reporting, but also to what pharmacovigilance is all about. Traditionally pharmacovigilance has been focused mostly on health care professionals as a target group, and to communicate with the general public as a target group required different approaches and sometimes also different skills.
Aim: In this lecture a brief overview will be given of the role of patients as contributors to pharmacovigilance, especially focusing on their role in

spontaneous reporting. In addition, attention will be given on how to raise awareness about the importance of pharmacovigilance and what means of communications can be used for this purpose. To illustrate these aspects, practical experiences from our centre will be shared with the participants.

O 23

Coordinating the WHO Drug Monitoring Programme: The Role of WHO Collaborating Centres

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The World Health Organization (WHO) is the United Nation's specialist agency for health. Amongst a range of health issues, the organization covers safety and vigilance of medicinal products via the WHO programme for International Drug Monitoring. In advancing its global health priorities and strategies, WHO works with a network of more than 700 Collaborating Centres (WHOCCs) that support implementation of mandated work. WHO works with 4 Collaborating Centres to advance pharmacovigilance (PV) in countries. Thanks to these Centres, the WHO PV programme has expanded in membership and in its scope of work, especially in those regions with weak infrastructures but a high burden of diseases.

The present talk will trace the growth of pharmacovigilance as a global partnership, value added and the roles and responsibilities of each of the partners; and how WHO will continue to exploit the WHO CC model while joining hands with other groups and initiatives to support pharmacovigilance worldwide.

O 24

Knowledge About Adverse Drug Reaction and Reporting Among the Healthcare Professionals in Bhutan

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Introduction: National pharmacovigilance centre (NPC) of Bhutan, under drug regulatory authority (DRA) became official member of WHO programme for international drug monitoring in December 2014.Despite trainings and awareness created by NPC the number of adverse drug reaction (ADR) reports sent to NPC is considerable low. Better understanding about ADR among the healthcare professional could improve the pharmacovigilance system.

Aim: The aim of this study is to investigate knowledge about ADR and ADR reporting among the healthcare professional, both modern and traditional medicine practitioner.

Methods: Cross sectional study was conducted, using validated self-administered questionnaire. The questionnaires were distributed to 670 healthcare professionals including Clinical doctors, Nurse, Pharmacist and Traditional practitioner from four referral hospitals. There are 12 questions on knowledge and 10 questions on knowledge about reporting. The collected response was analysed descriptively by using SPSS version 20.

Results: Overall response rate was 65 %, consisting Clinical doctors 94 (21.6 %), Nurse 257 (59.1 %), Pharmacist 52 (12.0 %) and Traditional practitioner 31 (7.1 %). For each professional Mean score ± SD score are presented in the (Table 1). Overall mean score of the knowledge on ADR among healthcare professional was 6.52 ±2.81 out of the maximum score of 12. Whereas, knowledge on ADR reporting among healthcare professional was 3.94 ± 1.89 out of the maximum score 10.

Table 1 Score and mean ± SD of healthcare professionals on knowledge about adverse drug reaction and adverse drug reaction reporting

	Type of Healthcare professional
(1) Knowledge on ADR	**Clinical doctor Nurse Pharmacist Traditional Practitioner**
Mean ± SD	7.48 ± 2.950 6.15 ± 2.475 8.15 ± 2.428 4.13 ± 3.181
Score	
Excellent (≥10)	25(26.6) 24(9.3) 18(34.6) 1(3.2)
Good (7–9)	42(44.7) 91(35.4) 19(36.5) 9(29.0)
Fair (5–6)	12(12.8) 78(30.4) 12(23.1) 2(6.5)
Poor (≤4)	15(16.0) 64(24.9) 3(5.8) 19(61.3)
(2) Knowledge on ADR reporting	**Clinical doctor Nurse Pharmacist Traditional Practitioner**
Mean ± SD	3.93 ± 1.809 3.75 ± 1.742 1.79 ± 0.750 4.00 ± 1.770
Score	
Excellent (≥8)	1(1.1) 8(3.1) 5(9.6) 0(0.0)
Good (5–7)	35(37.2) 66(25.7) 26(50.0) 13(41.9)
Fair (3–4)	38(40.4) 127(49.4) 15(28.8) 8(25.8)
Poor (≤2)	20(21.3) 56(21.8) 6(11.5) 10(32.3)

Conclusion: Clinical doctor and pharmacist have better knowledge on ADR but nurses and traditional practitioner were relatively low. In addition knowledge on adverse drug reaction reporting is low for the entire healthcare professional. This study indicates that the healthcare professional have good knowledge on adverse drug reaction but the national pharmacovigilance centre need to focus on enhancing the knowledge on reporting adverse drug reaction.

O 25

The Impact of ADRs on Patient's Quality of Life After Packaging Changes of the Drug Thyrax®

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Introduction: Adverse drug reactions (ADRs) may have a great impact on the patient's quality of life (QoL). There are several factors that may interact with QoL, like the severity of the ADR. There is little information

to what extent ADRs influence the patient's QoL and which factors are of influence.

End of 2013 the packaging of the drug Thyrax® (levothyroxine) has been changed from a brown glass bottle to a blister package in the Netherlands. The product has not been changed. The Pharmacovigilance Centre Lareb received about 1800 reports concerning ADRs that occurred after this packaging change, of which more than 90 % from patients.

Aim: This study aims to explore the impact of ADRs on the QoL of patients who reported an ADR in relation to the packaging change of the drug Thyrax® to the pharmacovigilance centre Lareb.

Method: Patients who reported an ADR in relation to the packaging change of Thyrax® until April 2015 were included. QoL before and after the ADR and factors that may influence the QoL were studied using a web-based questionnaire. Domains in QoL that were explored are physical, social, mental, daily activities and overall health status, using an adapted COOP/WONCA tool [1]. QoL was expressed on a 5-point scale: very good (1) to very poor (5). Data were analyzed using a dependent and independent sample *t* tests and one-way ANOVA. Statistical significance was based on $p < 0.05$.

Results: The questionnaire was sent to 1638 patients, the response rate was 71 %. Overall, there was a statistically significant difference for each domain of QoL ($p < 0.001$). Average difference in QoL before and after the ADR was −0.8 for physical, −1.2 for mental, −1.4 for daily activities, −1.3 for social and −1.3 for overall health status. Factors that influenced 1 or more domains in QoL were: severity and seriousness of the ADR, if the patient was still able to go to work, the recovery and duration of the ADR, gender, age and education of the patients.

Conclusion: For patients included in this study the experienced ADRs have a clear negative impact on the patient's QoL. Changes in QoL was seen for each domain. Overall QoL score decreased by 1 point on a 5-point scale. Several factors that influence the QoL were found. Due to the specific setting of this analysis, it is unclear to what extent the results can be generalized to ADRs in general.

O 26

Enforcing the Habit—the Role of Champions in Pharmacovigilance Education

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Introduction: Many ADRs go unreported. Ignorance of what and how to report was one of Inman's 'Seven Deadly Sins' [1]. A system of local reporting centres can improve reporting rates and provide a focus for reporters in a locality [2]. In the United Kingdom, five regions have pharmacovigilance (Yellow Card) centres.

Aim: To improve reporting by recruiting a "Yellow Card champion" in hospitals and primary care groups (CCGs).

Method: Yellow Card Centre Wales set up and trained 14 pharmacist champions in Welsh hospitals in November 2012 to provide information and help others to complete Yellow Cards. The reporting rate in Welsh hospitals subsequently increased (Table below). This encouraged the Yellow Card Centre West Midlands to appoint a new pharmacovigilance pharmacist in October 2014 with the role of recruiting champions both in hospitals and CCGs. We offer these champions generic learning materials which they can adapt and use locally; and invite them to educational meetings.

Results: We have recruited 17 pharmacists, 3 nurses and 6 consultants in hospitals and 7 pharmacists in CCGs as champions, and held one regional study day and many local visits.

Reporting rates changed in Wales for the period 2012–13 to 2013–14 and in the West Midlands for (July–September) to (October–December) 2014 (Table 1).

Table 1 Reporting rate changes in Wales and the West Midlands

Wales	Change 2012–13 to 2013–14	
Hospital pharmacists	+189 (+134 %)	
All other reports	+339 (+67 %)	
West Midlands	Change from (July–September) to (October–December) 2014	
	Area with champions N (%)	No champion N (%)
Hospital	+31 (+43 %)	−3 (−12 %)
Primary Care	+5 (+9 %)	+24 (+21 %)

Conclusion: The introduction of the Welsh scheme has been associated with a substantial increase in reporting. Hospital reporting rates have also increased in the West Midlands scheme in the first three months where champions were introduced. Local pharmacovigilance champions appear to help increase the number of reports.

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Parallel Session F—Emerging Sources of PV Data

O 27

Use of Social Media for Data Mining in Pharmacovigilance

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Introduction: Many patients do not report adverse events to regulatory agencies or manufacturers because they are unaware that they can or should. However, patients often discuss AEs in social media and in online communities, often describing concerns that may be different from what they discuss with their doctors. Data mining tools can be leveraged to derive insights from these unstructured online conversations in real-time, thereby providing safety reviewers with an additional resource for drug

safety information, and potentially ahead of data obtained from traditional pharmacovigilance channels. Methodological studies are needed in the nascent field of social listening for pharmacovigilance to understand reporting biases and define quantitative assessments.

Aim: To evaluate the potential for social media listening to be.

Methods: MedWatcher Social is a social media listening platform developed by Epidemico in partnership with the US FDA and the WEB-RADR consortium of European companies and health authorities. MedWatcher Social employs a Bayesian classifier, trained to recognize English discussions of adverse events in social media and remove spam and duplicates, obscure identifying information, to mine and classify publicly available data from Facebook, Twitter, and online patient forums. A vernacular-to-regulatory dictionary is used to translate colloquial phrases describing symptoms into MedDRA Preferred Terms. Social media data are then contextualized and augmented by data from traditional pharmacovigilance sources to determine the validity.

Results: As of June 2015, we have collected 54,307,314 social media posts mention a medical product name. 1,531,816 of these posts bare some resemblance to an adverse event (Proto-AEs) and 56,607 were further reviewed by a human analyst according to MedDRA coding guidelines. Social media data show concordance with AE data captured by traditional drug safety reporting channels and clinical trials. We have also detected discussion topics in social media that could contribute to medical products intelligence in ways that spontaneous and observational data typically have not (e.g., drug misuse, product quality issues, patient benefits).

Conclusion: More methodological research is warranted to develop signal detection methods appropriate for this novel data source. Collaboration with regulators is also needed to provide guidelines for monitoring social media for adverse events.

Data will be presented on specific product. An evaluation of how data may differ among product types (e.g., OTC products, devices and DTC products) and data sources will also be presented. Additional challenges to using social media for drug safety surveillance will be addressed.

O 28

Integrating Pharmacogenomics with Pharmacovigilance—Croatian Experience

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Introduction: Pharmacogenomics is the study of variations of DNA and RNA related to drug response. Integrating pharmacogenomics with pharmacovigilance (PhV) have substantial role in searching post-marketing adverse drug reactions (ADR) and in drug development. Information on genetic polymorphisms in drug-metabolizing enzymes and drug transporters is valuable when analysing the causal relationship between drug intake and dose related ADR.

Aim: To study the possible genetic associations with ADRs, as part of its pharmacovigilance program, the Croatian Agency for Medicinal Products and Medical Devices (HALMED) has piloted a project to collect DNA and phenotype data of ADR cases using the international standardized phenotypic criteria.

Methods. Besides the data from spontaneous adverse reaction reporting system, the clinical data routinely recorded in hospital settings provide additional opportunities for identifying and quantifying ADRs. Since 2010 we asked reporters of some ADRs to invite patients to participate in the study. Patients who agreed to participate and signed an informed consent form were included. We established biological sample repository in the University Hospital Centre Zagreb, Lab for pharmacogenomics (accredited according to ISO 15189); undertake genotyping to identify novel associations or validate findings in cohorts of patients with well-defined phenotypes.

Results: HALMED developed a method for informing physicians or pharmacists and their patients about a possible pharmacogenetic involvement in the pathogenesis of the reported ADR and for offering easy access to genotyping. DNA samples from patients with ADRs that have been collected and genotyped are shown in Table. An anonymized copy of the test results has been used for the interpretation of possible signals. Some study results have been published.

Table 1 Pharmacogenomics markers genotyped in patients with adverse reactions (ADRs) with certain drugs

Drug	Adverse drug reaction	Pharmacogenetic marker
Statins	Myotoxicity, hepatotoxicity	CYP2C9, CYP2C19, CYP3A4, SLCO1B1, ABCB1, ABCG2
Warfarin	Bleeding	CYP2C9, VKORC1, MDR1
Clopidogrel	Bleeding, ineffectiveness	CYP2C19, ABCB1
Dabigatran, rivaroxaban	Bleeding	CYP3A4, ABCB1
Antiepileptic drugs	Hepatotoxicity, tremor, hair loss, headache, vertigo, hypersensitivity,	CYP2C9, CYP2C19, CYP3A4, UGT2B7, ABCC2
Antipsychotic drugs	Acute extrapyramidal symptoms, parkinsonism, akathisia	CYP2D6, CYP3A4, DAT, D2R
Immunosuppressants	Gastrointestinal intolerance, bone marrow/ hepato/ nephro-toxicity	CYP3A4/5, UGT1A9, ABCB1, ABCC2, ABCG2, SLCO1B3, TPMT, ITPA, XO
5-FU, irinotecan	Myelosuppression, diarrhea, death	DPYD, UGT1A1, SLCO1B1
Tyrosine kinase inhibitors	Pancreatitis, rhabdomiolisys, headache, rush, pruritus	CYP2D6, CYP2C9, CYP2C19, CYP3A4, ABCB1, ABCG2
NSAID	Nausea, gastrointestinal intolerance, liver toxicity, bleeding	CYP2C9, CYP2C19, ABCC2,UGT2B7

Conclusion: PhV centres a valuable starting point for pharmacogenomic studies and may suggest investigations and subsequent individualized pharmacogenetic counselling after a reported ADR.

O 29

Factors Influencing Adverse Drug Reactions Reporting by Patients—A Cross-Sectional Study from Bulgaria

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Introduction: The direct reporting of adverse drug reactions (ADRs) by patients is an important topic in the world of pharmacovigilance. It was first introduced in Bulgaria in July 2012 following Directive 2010/84/EC. Due to the high rate of under-reporting there is need to determine the target group of patients who are more likely to participate in the system and report ADRs.
Aim: This study aims to analyse the factors influencing adverse drug reactions reporting by patients.
Method: A survey based on face-to-face interviews was performed the first half of 2014. 300 patients were asked to participate. They were interviewed with a standardized semi-structured questionnaire consisting of questions for social and health status, previous experience with an adverse drug reactions, knowledge of pharmacovigilance system. Factors such as parenthood, chronic diseases, pre-existing conditions were examined to determine possible influences. Descriptive statistics and nonparametric tests were used for the purposes of the analysis.
Results: A total of 211 patients were enrolled in the study with an overall response rate of 70%. 3 % of the respondents had children with chronic disease, 28 % suffered from some chronic disease themselves and 21 % were caregivers for chronically ill relatives. The number of women who reported to have had experienced ADRs is twice as higher as those of men ($p < 0.005$).The presence of children (with/without chronic disease) and elderly relatives with chronic disease is shown to be also a factor for better understanding of ADRs and willingness to report. The preferred contact points for this group of patients are marketing authorisation holders or physicians. Chronically ill patients have better knowledge of ADRs and claim to have reported ADRs more often than healthy respondents. All reported outcomes are statistically significant.
Conclusion: The typical Bulgarian "reporting patient" is a woman with a chronic disease; mother and/or caregiver for chronically ill relative who have had some previous experience of ADRs. Chronically ill patients are more willing to participate in the ADR reporting system. These groups should be the target concerning patient empowerment and involvement in the direct patient reporting.

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O 30

Adverse Drugs Reactions (ADR) Collected by Medical Staffed Ambulances: Pilot Study

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Introduction: In Paris area, emergency medical assistance is run by the "SAMU de Paris". Medical-staffed ambulances go directly to take care of any patient with an acute medical problem after an evaluation of the clinical situation made by phone.
Aim: Collection, analysis and evaluation of adverse drug events (ADR), whatever it is, acute intoxication, organ failure, allergy, and whatever its clinical presentation.
Methods: Every month, forms from all medical interventions performed daily by the SAMU de Paris, are analysed retrospectively by a physician trained in pharmacovigilance. The following information is available: patient's main characteristics, description of the medical event, main diagnosis, and outcome. If an ADR is present or even suspected, a copy of the form is made. The pharmacovigilance centres contact medical staff that took care of the patient to retrieve more information about the final diagnosis and the drug involvement. If a drug adverse effect is retained, the case is anonymously registered in the national database, and a specific letter is sent to describe and sum up the case.
Results: From January to March 2015, 100 cases of possible ADRs have been collected.

- 68 cases of ADRs have been immediately diagnosed and registered. The table describes the main ADRs received;

Main characteristics of ADRs collected with SAMU de Paris

	Number (% total)	Drugs suspected (more than one can be suspected)
Intentional drug overdose	27 (40)	Psychotropic (24) paracetamol (2) potassium (1) digoxin (1) methadone (1)
Bleeding	14 (20)	Oral anticoagulant (8) LMWH (4) antiplatelet (2)
Hypoglycemia	12 (18)	Insulin (12)
Anaphylaxis	6 (9)	Antibiotics (4) NSAID (2) neuromuscular blocker (1)
Miscellaneous	9 (13)	psychotropic (5) Antituberculosis agents (2) pain killers (2) antibiotic (1), corticoids (1)

- The drug causality is pending for 23 cases. The main effects observed are cardiovascular (cardiac arrest, bradycardia) (9), neurological (coma, confusion) (9), and various effects (malaise, skin reaction, digestive perforation, hypoglycaemia, renal failure);
- Forth last 9 cases, a drug implication has been definitely ruled out, with nondrug intake (5), and another causative agent for 4 cases: Illicit substances (2), food (2).

Conclusion: To our knowledge, this is the first time that serious adverse drug reactions are collected directly from the first step of emergency care, before hospitalization. Excepted intentional drug overdose for suicide attempts, the main ADRs observed are expected and evitable, such as bleeding with anticoagulants or hypoglycaemia with insulin. Further analysis on cardiovascular effects is pending.

O 31

The Effect of Regulatory Definitions on Mining Social Media for Adverse Events: A Real-World Examination

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Introduction: There is growing interest and sophistication in mining social media for possible reports of adverse events (AEs). There is also growing concern in determining how such activities should be interpreted in light of regulations on reporting AEs to regulatory authorities. Academic studies have been conducted to address the direct question of the utility of mining social media for AEs, but the interaction of methodologies with regulatory definitions determines what ultimately constitutes an AE report to Regulators.
Aim: To examine the impact of the operational definition of "reporter" on the number of discovered possible AEs in mined social media data, and to explore the real-world ability to obtain reproducible results using a single definition of "reporter" across different methodologies, by asking six different vendors to use their standard methods to answer common questions based on common definitions.
Methods: We recruited six vendors who stated they were capable of mining social media for possible AEs to participate in this effort. A list with a predetermined set of drugs was used, and vendors were requested to perform retrospective mining of social media for all possible AEs for each drug over a specified time period. A limited number of publicly-available social media sites were used with each vendor choosing the sites they would mine. Possible AEs were defined as containing all of the "Four Elements", i.e., an identifiable event, patient, drug, and reporter. Four separate definitions of reporter were used: Lenient (no requirement to identify a reporter), Low (any type of information suggesting there is a reporter); Standard (at least one piece of identifiable information for the reporter); Strict (existence of a valid email address plus another piece of identifying information).
Results: Results are currently being analysed. Preliminary results suggest that requiring a strict definition of reporter dramatically reduces the number of possible AE counts. Variations in vendor methods also affected the number of results, which made it difficult to compare across methods.
Conclusions: In mining social media for possible AEs, how "reporter" is defined will directly impact what qualifies for reporting to regulators. Unforeseen complications in interpreting results may arise from undisclosed assumptions used early in the data mining process. Variations in real-world methods also affected the number of results, to the extent that it appears a comparison across methods is not possible. More transparency is needed in methodology when performing mining for purposes of reporting.

O 32

Exploiting Heterogeneous Open Data for Pharmacovigilance

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Introduction: Given the importance to timely identify and track safety risks, the concurrent exploration of various types of data is essential. For post-market surveillance, these sources include spontaneous reporting systems, electronic health records, bibliographic databases, and even social media. This expansion in the search space of drug safety experts dictates the need for introducing appropriate query mechanisms and high-throughput data analytics to enable efficient knowledge extraction and management [1].
Aim: To develop a mechanism capable of: (a) querying diverse publicly available data sources upon a user's request comprising of a drug and a condition of interest, (b) aggregating the retrieved data, and (c) supporting their joint exploitation through visualization in a common timeline.
Methods: We elaborated on programmatic data access to: (a) FAERS, accessed through the openFDA Application Programming Interface (API), (b) PubMed, accessed via the Web services of Europe PubMed Central, and (c) Twitter, accessed through the respective search API. For each drug-event search, query expansion was applied based on synonyms and semantically-relevant terms obtained from drug information sources and standard terminologies. The data were aggregated, filtered and projected in a common timeline aiming to illustrate potential associations along time.
Results: We elaborated on a case study concerning new oral anticoagulants (for which data are available from all three sources) and the risk of cerebral haemorrhage. Synonyms for drugs (including brand/international names) and conditions (e.g. intracranial/brain haemorrhage/haemorrhage/bleeding /, etc.) were used in query expansion. The search was performed periodically within a 3-month period, to identify potential trends. Our preliminary analysis illustrated that the majority of Twitter posts concerned references to scientific publications, close to the date that these were indexed in PubMed. We did not obtain posts corresponding to personal opinions/experiences of potential patients. However, during the trial phase of the considered drugs, discussions among patients were identified concerning the alternative therapeutic option and the anticipated reduced haemorrhage risk. FAERS data illustrated a rather constant rate in reporting during the examined period.
Conclusions: This study concerned a proof-of-concept development for systematic access to diverse public data sources for pharmacovigilance.

The case study provided indications concerning the kind of data that are available in each source, the need to contextualize queries according to the data source used, as well as potential insights from visual inspection. Further analysis is underway, along with additional case studies.

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CIOMS Keynote Lecture

O 33

Beyond protection: The Iintegrity of Science as a Fundamental Ethical Concern

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Scientific research produces a unique social good, namely, the information and interventions needed to understand and address the health needs of people. The research enterprise is a complex set of coordinated activities involving diverse stakeholders, each of whom has powerful interests that can conflict with the social mission of science. Research ethics tends to focus on protecting the rights and welfare of one such stakeholder, namely, study participants. But this focus is insufficiently sensitive to the ways in which other interests of stakeholders, including some interests of study participants themselves, can threaten the validity and integrity of the research process. This talk describes a broader framework for thinking about research ethics and explores its implications for recent proposals to grant early access to novel interventions or to truncate the drug development process.

Parallel Session G—Hospital Pharmacovigilance, ADR reporting in patients and Clinical Epidemiology

O 35

Health Care Professional Perspectives on Adverse Event Reporting in the United States and Technology's Role

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Introduction: The underreporting of adverse drug events (ADEs) and the absence of specific product identifiers in ADE reports are an international health concern. Several studies have been conducted to assess the root causes. However, few studies have focused on the United States and the role of technology in reporting practices.

Aim: To identify causes for ADE reporting challenges in US hospitals and ambulatory settings.

Methods: Tufts CSDD conducted a survey assessing the process for reporting ADEs in hospital, ambulatory, and retail pharmacy settings. Survey respondents were asked about: their experiences reporting ADEs; the process for reporting AEs, including the role of health information technology; and their thoughts on the causes for not reporting ADEs. The survey was sent to individuals in internal and external databases via e-mail and social media. The survey was conducted from May 16, 2014 to August 21, 2014.

Results: A total of 284 individuals participated in the survey, with 123 individuals completing the survey. 51 % of respondents had not reported an ADE in the last five years. 53 % of respondents note that a lack of systems integration (i.e. hospital databases) was often or very often a main reason ADEs were not reported. Technology issues were particularly acute in the hospital setting. The majority of hospital-based respondents would access at least three systems as sources of information about ADEs (51 % of respondents) and suspect drugs (62 % of respondents) to manually complete an ADE report. Respondents indicated that less than 30 % of electronic systems in the hospital setting could track product-specific identifiers such as manufacturer, National Drug Code (NDC) or lot numbers.

Conclusions: This study has identified key factors that contribute to the underreporting of adverse drug events in the United States including the prevalence of technological gaps within electronic systems. In the hospital setting, we suggest that reporters should have adverse event reporting data, including specific drug identifiers, readily available to them via better integration of current databases.

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O 36

Triggers of Active Surveillance of Adverse Drug Events in Hospitalized Newborns: A Pilot Study

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Introduction: The population of newborns is usually not included in clinical trials for the approval of new drugs. In this context, drug therapy in children is based on extrapolation of information that lead to the approval of the drug for use in adults.

Aim: To improve the safety of medication use by infants, the study aims to use triggers to identify adverse drug events (ADEs) in hospitalized newborns.
Methodology: A triggers list of adverse drug events was developed by reviewing the literature and by consensus and experience of the clinical team of neonatology. A pilot study was conducted from 12.09.2014 to 30.01.2015, totalling 27 days of investigation. The triggers on this list were actively sought in medical charts of newborns, admitted to the neonatal intensive care unit of a medium complexity university hospital in Sao Paulo, Brazil. Newborns were followed until their discharge or until completing 29 days of life. We excluded those patients who did not use drugs during hospitalization.
Results: We included 19 newborns. Of these, 1 was excluded for not having used drugs during hospitalization. Of 50 triggers listed, 33 have detected ADEs. These triggers were identified 155 times in the charts and detected 32 ADEs. The drugs involved in ADEs were amikacin, amoxicillin, caffeine, cefotaxime, dobutamine, dopamine, phenobarbital, fentanyl, furosemide, midazolam, oxacillin, acetaminophen, penicillin and sildenafil. The ADEs detected were: increase in serum creatinine, diarrhoea, vomiting, hypophosphatemia, hypoglycaemia, hyperglycaemia, hyponatremia, increased blood pressure, hypotension, leukopenia, opioid withdrawal syndrome, chest tightness, neutropenia, oxygen desaturation, tachycardia, thrombocytopenia.
Conclusion: the use of triggers is useful for active surveillance to detect ADEs in hospitalized newborns.
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O 37

Strategies for Detection Adverse Drug Reactions—Comparison of Hospital Database and Spontaneous Reporting

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Introduction: Adverse Drug Reactions (ADR) are an important cause of patient morbidity, mortality and additional costs in health systems (Lazarou, Pomeranz et al. 1998). Spontaneous ADR reporting is used worldwide for post marketing surveillance of medicines. Since underreporting is its major limitation more effective strategies for ADR detection are needed (Salmeron-Garcia, Cabeza Barrera et al. 2010).
Aim: To identify, characterize and compare ADR detected through diagnostic codes of a hospital administrative database and through spontaneous reporting.
Methods: A retrospective study was conducted to identify and characterize the ADR, occurred in a central hospital in the north of Portugal, from January 1 to December 31, 2011. We used: (1) diagnostic codes of a hospital clinical-administrative database (CAD), obtained from the Central Administration of the Health System; (2) data from a chart review performed by medical coding auditors over a random sample of 11 % CAD episodes; (3) spontaneous reports of ADR received in the Northern Pharmacovigilance Centre (NPC), reported by health professionals. A descriptive analysis was performed for the following data: demographic information of the patient; ADR (coded with MedDRA); medicines (classified by the Anatomical Therapeutic Chemical Code).
Results: In the spontaneous reports the median age of the patient was 55 years and 67 % of the episodes were from females, while in the CAD chart review the median age was 65 years and 49 % were from females. In this study we identified 200 ADR from the 52 spontaneous reports, and 242 ADR over the 153 inpatient episodes chart reviewed, which corresponds approximately to 2274 ADR in all the 1438 inpatients episodes identified with either one external cause or one diagnosis of ADR found in CAD. The most affected "organ" by ADR was the skin and subcutaneous tissue disorders in both methods. The second most affected "organ" was general disorders and administration site conditions (face oedema) in spontaneous method, while in chart review the blood and lymphatic system disorders (bone marrow failure) was the second most frequent clinical problem related to medicines. In both methods the medicines most involved in ADR were antineoplastic agents (L01). We have found that only one of the 153 episodes of ADR detected by chart review was spontaneously reported to NPC.
Conclusion: Diagnostic codes of hospital administrative databases have the potential to detect episodes of ADR that were not reported to the regulatory authorities. Therefore, they can give an important contribute to the safety and the risk management of medicines.

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Implementation of Pharmacovigilance in Clinical Sitting: National Oncology Institute Experience

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Introduction: Adverse drug reactions (ADR) are underreported by hospital staff despite numerous efforts [1]. The obstacles of reporting are well

known [2]. A closer relationship and collaboration between hospitals and pharmacovigilance centres are suggested as mean of solving problems.
Since July 2014, the Centre Anti Poison et de Pharmacovigilance of Morocco (CAPM) has launched collaboration with the National Institute of Oncology INO to facilitate collection of all adverse events related to drugs used in cancer and to develop a pharmacovigilance regional unit at hospital setting.
Aim: To share the steps followed to implement pharmacovigilance in hospital level and to highlight the importance of local implementation to increase quality and quantity of reports and to improve signal detection.
Methods: We evaluated the impact of the training and developing capacity building of INO Staff by comparing two periods of one year before and after launching collaboration. We compared the number of reports, the Completeness, the quality of information reported; the number of signal detected and risk minimization action implemented.
Results: The results showed that all pharmacovigilance steps taught to the INO staff during training sessions, namely stages from collecting information until the risk minimization actions, have been assimilated and implemented at the hospital sitting.
Preliminary results of the comparison of the ADR cases collected from INO during two periods show a significant improvement in quality and quantity of reports, the final results will be available at the end of the chosen period [1 July 2014–1 July 2015].
Conclusion: Pharmacovigilance centers have a public health role in promoting patient safety, the development of the pharmacovigilance in each clinical sitting is a key element to ensure the security of patients.
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Parallel Session H—Herbals

O 39

Do We Need New and Specific Methods for Pharmacovigilance of Herbal Medicines?

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Herbal medicines (HM) adverse reactions are a public health problem worldwide. The need for pharmacovigilance for HM is essential for the identification and assessment of risks from the use of herbal products (questionable safety, efficacy and quality), which are not always tested with rigor, or often not subject to approval by regulatory agencies. Unfortunately, all pharmacovigilance tools and methodologies were developed for conventional drugs and in some conditions these tools are be applied with difficulty to herbal medicines.
The pharmacovigilance community consists mainly of physicians and pharmacists who are not aware enough of this problem because of their university studies which underestimates the seriousness and emergency interest with regard to HM.
Faced with an adverse reaction to a HM, how should this case be handled from the pharmacovigilance perspective? Which pharmacovigilance tools and methodologies should be used? HM have their own specificities that are completely different from conventional drugs. These specificities are related to the ways in which these products are named, perceived, sourced and utilized.
This lecture will discuss all stages of pharmacovigilance (data management, recording and coding the identity of HM, classification, causality assessment, signal detection, regulation) related to adverse events from HM to answer to the question: "Do we need new and specific methods for pharmacovigilance of herbal medicines"?

O 40

Impediments in the Monitoring of Drugs of Traditional System of Medicine

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Introduction: India has started a National Programme for monitoring of ASU (Ayurveda, Siddha and Unani) drugs in 2008. Together with Allopathic medicine, Ayurveda, Siddha and Unani medicines are practiced in India as non-allopathic systems. These systems comprise a wide range of therapeutic approaches that include diet, herbs, metals, minerals, precious stones and their combinations as well as other non-drug therapies. Ayurveda is the most commonly practiced system of medicine particularly in rural India, where 70 % of the population lives.
Methods: To assess the authenticity and importance of temperament in selecting drugs in the Unani system a study was conducted with the association of Department of AYUSH, Government of India at an Apex Medical Hospital. A formulation consisting of 5 medicinal plants, Adhatoda vasica Nees (leaves), Piper longum (fruits), Picrorhiza kurroa (root), Hyossypus officinalis Linn (flower), Linum usitatissimum Linn (seed) was prepared in a tablet form as per Unani pharmacy.All five ingredients used in Unani system of Medicine are of hot and dry temperament. A total of 576 patients of either sex in the age group of 15–45 years suffering from bronchial asthma and having more than 15 % increase in FEV1 following administration of inhalation β2 agonist drugs were included in the study and received a dose of 500–1000 mg TDS. The exclusion criteria were diabetes mellitus, pregnancy, h/o myocardial infarction, severe hepatic or renal damage and patient on steroid therapy. The temperaments of the patients were 'Cold and Moist (Balghami) (n = 236), 'Hot and Moist' (Damvi) (n = 150), 'Hot and Dry' (Safravi) (n = 118), and 'Cold and Dry' (Saudavi) (n = 72). . Spirometry was done on 0, 7, 15, 30 and 90th days.
Results: The efficacy of the formulation was found to be different in patients of different temperament, being maximum in the patients with 'Cold and Moist' (Balghami) temperament and least in Saudavi and Safravi temperaments Further, the adverse drug reactions, though mild in nature and mostly confined to gastrointestinal and central nervous systems were fewer in the patients with opposite temperament to the drug.
Discussion: From pharmacovigilance point of view, use of herbs as a single drug or in combination with others pose problem for monitoring.

This study was done on a small number of patients and only one drug formulation. More such studies are required to validate the traditional concept.

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Acute Hypersensitivity Reactions to Herbal Remedies in Children Reported to the WHO VigiBase® Database

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Introduction: The use of herbal medicines in children and the general population is continually on the rise with an overall herbal lifetime and current use ranging between 0.8–85.5 and 2.2–8.9 %, respectively. Contrary to many parents' belief, herbal products are not always a safe alternative to conventional drugs and can cause a variety of adverse reactions including hypersensitivity (2). Although acute hypersensitivity reactions are generally considered to be rare, little knowledge exists on the frequency and type of these reactions especially in specific population groups like children.
Aim: To assess patterns of acute hypersensitivity reactions to herbal medicines reported to the WHO global individual case safety report (ICSR) database VigiBase® in children.
Methods: From the original VigiBase® extract for the time between 1968 and August 2014 we included all reports where WHO–ART reaction terms that are indicative of acute hypersensitivity reactions were associated with a herbal ATC code and classified as "suspect" with a "certain", "possible" or "probable" causality assessment, a latency time of 0 or 1 day, and age was below 18 years.
Results: VigiBase® contained 2,646 ICSRs with 14,860 distinct adverse reactions reported in association with herbal medicine in children. Among those, 150 cases with 222 allergic reactions met our inclusion criteria. The most commonly reported WHO–ART terms were Urticaria or Rash (41.4 %), Anaphylactic or Anaphylactoid reaction (16.2 %), Asthma, Stridor or Bronchospasm (9.0 %), Anaphylactic shock (5.4 %), Allergic reaction (5.4 %), and Oedema mouth (5.4 %). The most frequently reported suspect herbals were mixed herbal products (31.2 %), herbal pollen (29.7 %), Phleum pratense (13.1 %), and Hedera helix (7.2 %), accounting for 82.0 % of all included reports. Most frequent routes of administration were oral (39.2 %), subcutaneous (29.7 %) and sublingual (13.1 %). Eight out of 12 cases of anaphylactic shock were related to herbal pollen (6 subcutaneous). Slightly more reports were on males than females (54 % vs. 46 %) and 62.6 % of cases were reported in the age group of 10–17 years. The majority of reports were received from Germany (28 %), Sweden (15.3 %) and Thailand (11.3 %).
Conclusion: VigiBase® contains a considerable number of acute hypersensitivity reactions in children associated with herbal medicines, including life-threatening reactions such as anaphylactic shock. It is a valuable resource for their documentation and analysis of reporting patterns. Further studies are needed to determine the frequency of hypersensitivity reactions to herbal medicines and to identify possible risk factors.

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Safety of Red Rice Yeast Food Supplements

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Introduction: Red yeast rice (RYR), also known as "red Koji" or "Hongqu", is a remedy from the Traditional Chinese Medicine, largely used in Western countries. It is produced by fermenting steamed rice with a food fungus, M. purpureus (Aspergillaceae family). The lipid-lowering properties of RYR are due to its content in monacolins, a family of naturally occurring substances that inhibit hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase. The total content of monacolins in RYR is usually in the range of 0.4 % w/w; about 90 % of this consists of monacolin K which is chemically identical to lovastatin. The popularity of RYR is due to the perception that is of natural origin and then, by definition, safe. Nevertheless in the literature cases of adverse reactions following RYR consumption have been published.
Aim: To describe suspected adverse reactions (ARs) associated with food supplements containing RYR.
Methods: Spontaneous reports of suspected ARs to natural health products are collected in Italy within the Italian Surveillance System of suspected adverse reactions to Natural Health Products coordinated by the National Institute of Health, in collaboration with the Italian Medicines Agency and the Ministry of Health.
Results: From April 2002 to May 2015, 50 reports of suspected ARs to RYR were collected. The mean age was 64 years, 73 % of reports were related to females. The most frequent reported reactions were: myalgia and/or creatine phosphokinase increase (CPK) 18 reports (36 %); gastrointestinal reactions in 12 (24 %) cases and liver injury in 9 reports (18 %). Eleven patients were hospitalised, among these one case of rhabdomyolysis was reported.
Conclusions: In Italy sales data of food supplements are not available and reporting rates cannot be estimated. However, our results suggest that the risk profile of food supplement containing RYR is comparable to that observed for synthetic statins. In Italy the Ministry of Health in 2003 allowed a maximum dose of 3 mg/day of monacolin K in food supplements, to assure the safety of the products however, in 2012 the European Union increased this dose to 10 mg/day. It is to be underlined that a dose of RYR containing about 5–7 mg of monacolin is as effective as 20–40 mg of pure lovastatin, so allowing a dose of 10 mg of monacolin in RYR based supplements could expose patients to a higher risk of adverse events. For this reason, continuous monitoring "natural" products safety is mandatory.

Parallel Session I—Hot Topics Around the Cube (Selection of the Best Abstracts)

O 43

Drug-Induced Liver Injury: Where Are We in 2015?

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Idiosynchratic drug-induced liver injury (DILI) is still in 2015 one of the most frequent causes to terminate a drug development programme, the leading cause of acute liver failure in the US, box warnings and drug withdrawal from the market. As such it remains a major concern in Public Health. Progress has been made in the early detection of liver toxicity in clinical trials by using Hy's Law although this rule needs to be better understood. In practice the usual biomarkers of the liver injury are the same ones but their use need to be clarified and several initiatives such as SAFE-T in Innovative Medicines Initiative (IMI) are ongoing to determine the value of new and early biomarkers of DILI. DILI classification based on the R-ratio is now widely adopted and has been shown as a robust prognostic factor. The diagnosis of DILI is based on the exclusion of the non-drug causes of acute liver diseases which is the main challenge if the right investigations are not standardised through a flowchart and performed at the onset of the liver injury. RUCAM is widely used as causality assessment method although it is criticized for interobserver variability. RUCAM update and improvements are ongoing in order to provide a powerful tool for healthcare professionals. DILI risk factors are better known based on epidemiological and chemical studies that recently brought new evidence to be taken into account early in drug development programmes. The various and complex mechanisms for DILI have been deeply investigated expanding our knowledge on the main determinants. Despite several attempts with new in vitro models it is still rather hard to predict hepatotoxicity in humans. However pharmacogenetics, toxicogenomics and proteonomics including significant investments in bioinformatics made dramatic progress and will certainly bring more reliable results in clinical and preclinical studies.

O 44

Cohort Study of Blood Dyscrasias Associated with the Use of Proton Pump Inhibitors (PPIs)

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Introduction: Blood dyscrasias, such as agranulocytosis, haemolytic anaemia, aplastic anaemia, and thrombocytopenia, are serious conditions that may be induced by the use of drugs. Different case reports associated the use of Proton pump inhibitors (PPIs) with the occurrence of blood dyscrasias. In 2007, the European Medicines Agency reviewed the safety of lansoprazole because of an unexpected number of haemolytic anaemia cases. The signal was monitored over time and it was deemed necessary to evaluate in epidemiological studies the possible causal role of PPIs in the development of blood dyscrasias.
Aim: This study aimed at describing the incidence of blood dyscrasias among PPIs users and estimating the risk increase associated with current use of different PPIs.
Methods: A cohort study was conducted in the Umbria region (about 900,000 inhabitants), Italy. All subjects who received at least one prescription of PPIs (ATC code: A02BC) in the period 01 January 2002–30 June 2013 were included and followed from the incident prescription up to the first of the following events: hospitalization for blood dyscrasias (ICD-9 codes 283, 284, 287, 288), transfer from the region, death, end of the study. Each individual's observation time was divided into exposure periods: "current use" according to the duration of the prescription; "recent use" defined as the 60 days after the end of the current period; and "non-use" for the following days up to a subsequent prescription or the end of the study period. A nested case-control study was performed to control for confounding factors such as concomitant use of antibiotics, NSAIDs and antiplatelet drugs in the 30 days preceding the hospitalization date.
Results: A great increase (+135 %) in the prevalence of use of PPIs was observed in the study period: in 2002 about 8.0 % of the population received at least one prescription of PPIs. This proportion increased to 18.7 % in 2012. Users of PPIs had a median age of 68 years and were more frequently female (M/F ratio = 0.8). The median duration of treatment was 72 days, with 27 % of the users receiving only one prescription during the year.
Conclusion: Data analysis is currently ongoing and estimates of the association between PPIs and the occurrence of blood dyscrasias will be presented.

O 45

Effect of Glyburide Compared with Other Second-Generation Sulfonylureas on the Risk of Cancer in Patients with Type 2 Diabetes Mellitus

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Introduction: Sulfonylureas have been associated with an increased risk of cancer when compared with other oral anti-diabetic agents. However, this effect may not be uniform across all sulfonylureas with some observational studies reporting an elevated risk with glyburide, in contrast to other second-generation sulfonylureas.
Aim: To determine whether the use of glyburide, when compared with other second-generation sulfonylureas, is associated with an increased risk of any cancer, and to assess whether the risk varies with cumulative duration of use and cumulative dose.
Methods: The U.K. Clinical Practice Research Datalink was used to conduct a cohort study among 52,600 patients newly-prescribed glyburide or other second-generation sulfonylureas between January 1, 1988 and July 31, 2013, with follow-up until July 31, 2014. Exposure to glyburide was treated as a time-varying variable, which was lagged by one year to account for latency and minimize reverse causality. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) of any cancer associated with the use of glyburide when compared with the use of other second-generation sulfonylureas. Secondary analyses were conducted to determine whether the association varied with cumulative duration of use (total number of months of exposure, classified into the following four categories: <12 months, 12 to 24 months, 24 to 36 months, and >36 months of use) and cumulative dose [expressed in defined daily dose (DDD) and classified into the following four categories: less than 365, 365 to 730, 731 to 1096, and >1096 DDDs]. All models were adjusted for relevant potential confounders, which included smoking, body mass index, and comorbidities.

Results: During 253,869 person-years of follow-up, a total of 4105 patients were newly-diagnosed with cancer (incidence rate: 16 per 1000 person-years). Overall, when compared with the use of other second-generation sulfonylureas, the use of glyburide was not associated with a significant increased risk of any cancer (HR: 1.09, 95 % CI: 0.98–1.22). In secondary analyses, duration-and dose-response relationships were observed, with longer cumulative durations and cumulative doses associated with an increased risk of any cancer (>36 months, HR: 1.21, 95 % CI: 1.03–1.42 and >1096 DDDs, HR: 1.27, 95 % CI: 1.06–1.51, respectively).
Conclusions: In this population-based cohort study, longer cumulative durations and higher cumulative doses of glyburide were associated with an increased risk of cancer. These findings support the hypothesis that glyburide may be associated with an increased risk of cancer, when compared with other second-generation sulfonylureas.

O 46

Challenges of Evaluating the Safety Profile of Non-active Implantable Medical Devices Compared to that of Medicinal Products

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Introduction: Recent safety issues involving non-active implantable medical devices (NAIMD) have highlighted the need for better pre-market and post-market evaluation [1–2]. Some stakeholders have argued that certain features of medicinal products safety evaluation should be applied to medical devices.
Aim: To compare the current process and methodology for the assessment of the safety profile of NAIMD with that of medicinal products in order to identify potential gaps and make recommendations for the adoption of new methodologies for the ongoing benefit/risk monitoring of these devices throughout their entire life cycle.
Methods: A literature review served to examine the current tools for the safety evaluation of NAIMD and that of medicinal products. We searched MEDLINE using these two categories. We supplemented this search with Google searches using the same key terms used in the MEDLINE search.
Results: By means of a comparative approach, we summarized the new product design, development cycle (pre-clinical and clinical phases), and post-market phases for NAIMD and drugs. The respective processes to integrate and assess the safety data during the life-cycle of the products, including signal detection, signal management and subsequent potential regulatory actions were also evaluated and compared.
The search identified a gap in NAIMD safety signal generation: there is no global program to collect and analyse adverse events and product quality issues. Data sources in real-world settings, such as electronic health records, need to be effectively identified and explored as additional source of safety information, particularly in some areas like the EU and USA where there are plans to implement the unique device identifier (UDI). The UDI and other initiatives will enable a more robust follow-up and assessment of long-term patient outcomes.
Conclusions: The safety evaluation system for NAIMD is different in many ways from that of drugs, but both systems face analogous challenges with respect to monitoring real-world usage of the products. There are certain features of the drug safety evaluation process that, when adopted and adapted for NAIMD, can lead to a better and more systematic evaluation of the latter.
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Parallel Session J—New Methodologies in Signal Detection and Safety surveillance

O 47

Multivariate Analysis for Visualizing Pharmacovigilance Data

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Introduction: Routine pharmacovigilance involves on-going reviews of suspected adverse drug reaction reports. In the typical scenario safety analysts review frequency lists of drug-event pairs-i.e. lists of univariate reporting relationships. Given that adverse event reports very often involve multiple drugs and event, the interest in understanding and comparing overall drug safety profiles, the interest in detecting and understanding drug-induced syndromes and drug–drug interactions, and ongoing challenges related to duplicate reporting, multivariate statistical methods may be attractive but underutilized tools.
Methodology: We take a case studies approach to presenting potential opportunities for the application of MVA to visualize and understand drug safety data. The methods considered include hierarchical cluster analysis, correspondence analysis, metric multidimensional scaling, factor analysis and discriminant analysis. We present MVA and corresponding visualizations in a few areas of interest in pharmacovigilance including drug abuse potential, severe cutaneous adverse reactions (SCARs,), and drug abuse potential.
Results: By allowing for the visualization of the geometric position of drugs in a complex adverse event space, one or more forms of MVA and visualization enhanced understanding of pharmacovigilance data including the scheduling of drugs for abuse potential, the relationships between SCARs, and supporting manual reviews for duplicate reporting.
Discussion: MVA have potential to enhance understanding and presentation of pharmacovigilance data. However there are substantial limitations to be considered. The well documented and substantial limitations of spontaneous reports are not neutralized by MVA, and some of the usual limitations of these data take on added significance with MVA. Finally depending on the method selected MVA entails various assumptions, the

violations of which can have significant consequences. However it seems that these methods are worth exploring further as additions to the pharmacovigilance toolkit.

O 48

WEB-RADR: Use of Mobile Technologies and Social Media in Pharmacovigilance

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Introduction: The WEB-RADR Project seeks to harness new technologies including social media and mobile apps with the aim of enhancing pharmacovigilance through these new methods of communication. WEB-RADR comprises world-leading experts from industry, regulatory agencies, and academia who's expertise will ensure that the tools developed are effective and support pharmacovigilance practices in the EU network. Such expertise will also prove invaluable in carefully evaluating the scientific value of the tools, and subsequently forming the relevant regulatory frameworks for their use.
Project outputs: The project is developing a mobile app for patients and healthcare professionals to report suspected adverse drug reactions to national EU regulators, and investigating the potential for publicly available social media data for identifying drug safety issues. Reports received via the mobile app will be compared to those received via established reporting schemes for completeness, quality and value for detection of safety issues. Publicly available social media data will be evaluated for its utility in signal detection and strengthening.
Results: The UK version of the mobile reporting app will launch in July 2015. The presentation will cover the experiences of early adopters of the app, feedback and reports received and an indication of the development pathway for the future. In addition is will cover the early outputs social media of the analysis of social media data to contextualise the work of the project.

O 49

Tuning Epidemiological Study Design Methods for Exploratory Data Analysis in Real World Data

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Introduction: Many methods have been proposed for signal detection in observational longitudinal databases. It is unclear which methods are best and specifically the value of methods designed for epidemiological studies, re-purposed for hypothesis generation.
Two methods widely used in pharmacoepidemiology are the High Dimensional Propensity Score (HDPS) and Self Controlled Case Series (SCCS). Both methods aim to reduce the impact of confounding, but with different approaches. HDPS is a semi-automatic method that looks to balance comparator drug characteristics to an exposed population group before computing risk estimates across the two groups. SCCS looks to compare the rate of an event when exposed compared to unexposed—but both exposed and unexposed time are taken from the same patient at different time points.
Aim: To examine the performance of HDPS and SCCS in a hypothesis generation framework for more recently approved medicinal products.
Methods: HDPS and SCCS method performance was examined for the antidepressants desvenlafaxine and escitalopram and the Rheumatoid Arthritis product, adalimumab. Analyses were performed on both the UK EMR THIN and the US insurance Claims database Optum. For antidepressant analyses, duloxetine was a comparator, and the following outcomes: hypertension, orthostatic hypotension, proteinuria, hyperlipidemia, and fractures. For adalimumab we used the drug class as comparator and looked at: Acute Myocardial Infarction (AMI), GI Perforation, Herpes Zoster, Interstitial Lung Disease, Lymphoma and Pneumonia.
For HDPS we used a new user design, varied definition of time and propensity score matching approach (logistic regression, SMR methods, none). For SCCS we looked at all occurrences versus first occurrence of outcome, and varied time at risk, and required enrolment period.
Results: Signals of disproportional recording (SDRs) were seen for each of the outcomes in the study however performance varied by design choice, by method and database. For SCCS inclusion of only first outcome led to more effective highlighting of SDRs. Surveillance window variation and enrolment period had limited impact. Differences in HDPS outputs were seen as case definition varied, and sometimes by method of PS matching which were explicable by apparent differences in demographic characteristics between the treated and comparator populations.
Conclusions: This study supports the promise of Epidemiological methods for signal detection in observational databases of EMRs and Insurance Claims. Specific challenges and discordance of outputs observed across parameter settings, suggest work is needed to optimize their performance where routine approaches operationally may need to differentiate by drug, disease, data set and healthcare system.

O 50

Spontaneous Reports and Electronic Health Records for Safety Signal Detection—Yin and Yang

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Introduction: Spontaneous reporting systems (SRSs) remain the cornerstone of post-marketing drug safety surveillance despite their well-known limitations. Judicious use of other available data sources is essential to enable better detection, strengthening and validation of signals.
Objective: In this study we investigate the potential of electronic healthcare records (EHRs), to be used alongside SRS, with the aim to improve signal detection.
Methods: A signal detection strategy focused on a limited set of adverse events deemed to be important in pharmacovigilance was performed

retrospectively in two data sources: (1) EU-ADR database network and (2) EudraVigilance SRS database using data between 2000 and 2010. Five events were considered for analysis: (1) acute myocardial infarction (AMI); (2) bullous eruption; (3) hip fracture; (4) acute pancreatitis; and (5) upper gastrointestinal bleeding (UGIB). Potential signals identified in each system were verified using current published literature. The complementarity of the two systems to detect signals was calculated as percentage of unilaterally identified signals out of the total confirmed signals. As a proxy for the associated costs, the number of signals that need to be reviewed to detect one true signal (number needed to detect: NND) was calculated. The relationship between background frequency of events and capability of each system to detect signals was also investigated.

Results: The contribution of each system to signal detection appeared to be correlated with the background incidence of the events, being directly proportional to the incidence in EU-ADR and inversely proportional in EudraVigilance. EudraVigilance was particularly valuable in identifying bullous eruption and acute pancreatitis (71 and 42 % of signals correctly identified from the total pool of known associations, respectively) while EU-ADR was most useful in identifying hip fractures (60 %). Both systems contributed reasonably well in the identification of signals related to UGIB (45 % in EudraVigilance, 40 % in EU-ADR), but only fairly for signals related to AMI (25 % in in EU-ADR, 20 % in EudraVigilance). The costs associated with detection of signals were variable across events; however, it was often more costly to detect safety signals in EU-ADR than in EudraVigilance (median NND = 7 vs. 5).

Conclusions: EHR might have additional value as source for signal detection, alongside already established systems, especially in presence of adverse events with high background incidence. While SRS appeared to be more cost-effective overall, for some events the costs associated with signal detection in EHR might be justifiable.

O 51

Adverse Event Cluster Analysis for Syndromic Surveillance

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Introduction: Syndromic surveillance is used in disease outbreak detection to identify illness clusters early, before diagnoses are confirmed and reported. An early application in pharmacovigilance was the use of a recurrent neural network for syndrome detection in VigiBase [1]. Subsequent research indicated that latent class models may perform better, but that lack of resolution and instability of the identified partitioning would impede adoption for real-world use.

Aim: To explore the potential for syndromic surveillance in pharmacovigilance.

Methods: We analysed 16,323 reports of risperidone with two or more co-reported adverse event terms, in VigiBase as of Jan 1 2015. Through cluster analysis based on reported adverse events terms, a natural partitioning of reports was sought. Technically, we assumed a latent class model with independent binomial distributions for adverse events, conditional on report class. So-called expectation-maximization was used to optimize the allocation of reports to classes while determining the adverse event profiles for each class. This was repeated 100 times and the individual solutions rank ordered by penalized likelihood. Consensus clustering based on the best 50 individual solutions yielded a wisdom-of-the-crowd partitioning.

Results: We identified 35 classes with at least 5 reports. In total, these comprised 15,012 (92 %) of the analysed reports. The three largest classes reflected, in turn, worsening of the underlying condition with symptoms such as agitation and aggressiveness, a spectrum of extrapyramidal adverse events, and disorders of the female endocrine system such as hyperprolactinaemia and non-puerperal lactation. Beyond that, it uncovered less expected patterns such as eight reports relating to increased intracranial pressure with signs and symptoms including papilloedema, diplopia, and headache.

Consensus clustering markedly improved stability compared to relying on the single best solution: it decreased the proportion of report pairs that were clustered together in one but not the other of two repeated analyses from 4.1 to 0.6 %. In addition, it increased the resolution of the identified classes, for example by sub-dividing the genitourinary adverse events into sexual dysfunction and urinary symptoms.

Conclusion: Syndromic surveillance for risperidone in VigiBase reliably recalled known disease spectra, while uncovering unexpected adverse event patterns requiring further review. Consensus clustering was valuable to secure more stable and precise results.

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Keynote Lecture 4

O 52

Role of Genomics in Pharmacovigilance

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Number of adverse drug reactions belong among traditionally classified as idiosyncratic reactions with no obvious relationship to the product's pharmacological properties, but with expected inherited risk predispositions. Recent advances in genomics, achieved over the past 15–20 years, partly opened the door towards "semi-personalized medicine", and also improved our understanding of these adverse drug reactions. For example striking associations between some HLA alleles, and drug-induced hypersensitivity reactions drug have been described. Predictive genetic testing for a few drugs has subsequently been introduced. Variability in drug metabolizing enzymes, receptors or signal transduction pathways also allow to stratify patient population with respect to risk of development of adverse reactions in some situations. Successful examples of the use of genomics in clinical medicine are summarized. However, the potential of genomics is still likely to be underutilized. This is partly due to the fact that for medicines authorized prior to year 2000 there was usually no PGx testing procedures available during drug development, partly due to relative lack of high quality pharmacogenomic studies in public domain. Furthermore, conservative attitude towards new procedures in drug utilization and lack of the use of electronic health records with decision-support tools make the use of genomics currently limited.

Bengt Erik Wiholm Lecture

O 53

Patient Safety Through Dialogue—How to Better Connect Pharmacovigilance and Healthcare?

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Introduction: Communication about benefits and risks of medicines is fundamental to ensuring the safe and effective use of medicines and implementation of risk minimisation measures. In order to further develop risk communication as part of the pharmacovigilance process and improve the impact of communication in terms of patient and public health, ISoP's special interest group CommSIG was established in 2013/14 and now invites the conference participants to its first interactive discussion session.
Aim: The session will present latest initiatives in the field from Europe and specifically discuss challenges and options around communication of risk factors for adverse reactions, with a view to how communications can connect pharmacovigilance activities and healthcare in various world settings.
Methods: There will be four short lectures from two pharmacovigilance specialists and two experts from outside pharmacovigilance, one from healthcare research, the other from communication psychology and medical decision-making. This will be followed by a discussion with conference participants, focussing on risk factors. While advising on risk factors is a major risk minimisation strategy in product information and risk management plans, little is known how these are best communicated for informed choice and successful risk minimisation.
Results: The session should result in identifying the challenges and options around communication of risk factors for adverse reactions, as well as open questions and learnings from the general field of health communication.
Conclusion: The results and initial recommendations will be made available as a report.

O 54

Healthcare Professionals' Perspectives On Regulatory Safety Communication About Medicines: The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action

P.G.M. Mol[1] on behalf of SCOPE work package 6[2]

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Introduction: Effective communication of safety information on medicines to healthcare professionals is essential for achieving the objectives of pharmacovigilance. Safety communications enable informed decision-making and allow healthcare professionals to give clear and useful information to their patients [1]. Currently, it is unknown how European healthcare professionals evaluate such safety communications.
Aim: To establish the usefulness and effectiveness of safety communications on medicines as well as opinions and preferences from the perspective of healthcare professionals in Europe.
Methods and Results: A web-based survey was developed in the context of the SCOPE project—Work Package 6 (risk communication) to assess the perspectives of healthcare professionals in Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and the UK. The survey assessed different means of regulatory safety communications with special attention to Direct Healthcare Professional Communications, national regulatory agency communications and educational materials. The survey in Norway and Sweden did not include educational materials. An official translation agency translated the developed, English survey and involved researchers in the different countries performed the back-translation. The different versions were pretested in each country. Based on the translation procedures and the pilot-testing, minor changes were made in the different versions to assure that their meaning was equivalent to the original English version. Healthcare professionals included in the study were general practitioners (GPs), cardiologists and pharmacists. In Spain and Sweden, only GPs and cardiologists were included. In most of the countries, healthcare professionals were recruited via an e-mail sent by professional bodies or through information on the website and/or in a newsletter of the national regulatory authorities. Descriptive statistics will be used to describe demographic characteristics of the respondents and to describe the preferences and experiences of the healthcare professionals with respect to the safety communications. Currently, data collection is ongoing.
Conclusions: The results of this study will reveal information on the appreciation of the currently used safety communication tools in Europe and will provide best practice recommendations to national regulatory authorities for communication strategies on the safety of medicines.
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O 55

Overview on Risk Communication in EU-Highlights from Croatia as Regional Example

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Introduction: The new EU Pharmacovigilance legislation enabled the possibility to identify much quicker safety concerns for marketed medicines in the Community and the risk communication about these findings is of most importance. The example of risk communication in Croatia will be given.
Aim: Croatia as a small to middle-sized market and the availability of local qualified persons for pharmacovigilance of Marketing Authorization Holders (MAH) enable a fast and coordinated risk communication to healthcare professionals, patients and the public. When safety concerns are

communicated it is very important to have a clear and straight forward massage from all MAHs with the same active substance of concern and the regulator to the one who should implement the warnings or restrictions to every days' practice.

Results: The national regulator for medicines—the Croatian Medicines Agency-HALMED has developed a method for informing physicians or pharmacists and their patients about specific safety concerns through individualized letters as a part of an answer to ADRs which they have reported will be explained. Additionally, two cases of coordinated risk communication within 10 MAHs for Quetiapine with additional combined PAS of measuring the impact of introducing educational materials for prescribing physicians and within 5 MAHs in the case of Combined Oral Contraceptives (COC) will be shown. The case of a public campaign performed in 2012 about the importance of reading the Patient information leaflet (PIL) for important messages for safe use of medicines and the case of introducing the importance of reporting and recognition of adverse drug reactions in the chronic use of antiepileptic medicines through a theatre play for children will be presented.

Conclusion: The national medicines regulatory authority plays an important role in disseminating the safety massages concluded at the EU level in coordinating the national MAHs in giving a harmonized message to the HCPs and patients not confusing them with similar but not unified safety information for the same active substance but different brand names medicines. This information is the most important step to reach one who finally uses the medicine and today there is a lot of discussion going on how to do this in the most proper way. This is an example how risk communication can be performed in a small to middle-sized country.

O 56

Talking About Harm and Benefit Information—The Challenges in Healthcare Practice

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Effective pharmacovigilance increasingly depends on patients playing their part, but the 'dialogue' is impeded because of patients' lack of knowledge of drug development and safety measures. However, the main barrier is the language we use, which is not the language of the man or woman in the street. Even many grass roots health professionals struggle to describe what 'pharmacovigilance' means—it is meaningless to patients. What words would they understand to describe the process?

Equally we talk about benefit/risk, whereas what we mean is the chance of benefit and the risk of harm. Pharmacovigilance should allow the patient and prescriber to understand the benefit/harm balance for a medicine and decide if it is right for them—but we currently only given them numerical information about the risk of harm ('affects less than 1 in 10 people')—and nothing about the chance of benefit. This means a truly informed decision is not possible. So, how can we best describe numerically the chance of benefit, and where can we source that information?

User testing of patient information leaflets is helping to make such leaflets fit-for-purpose, but wordings imposed by regulators are not tested. The wording associated with the Black Triangle initiative is a case in point: 'Warning—this medicine is subject to additional monitoring' means something quite different to some lay people—they think it means that they will have more tests or checks (monitoring) if they take the medicine. Equally the wordings recommended by PRAC appear less than ideal, and are un-tested.

Finally, Risk Management Plan summaries are designed to inform lay people about how the plans for safe use of medicines have been developed and put into practice. But what does user testing of RMP Summaries show? Are they fit for purpose?

This presentation will draw on academic research from the University of Leeds on describing benefit and harm information for patients, along with practical examples from user testing in practice by Luto Research, a spin out company of the University.

O 57

Risk Factors, Psychology and Communication

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Statistical illiteracy in health—the inability to understand health statistics—is widespread among the general public and among medical experts. For many people, it is generally hard to accept uncertainty, and even if they do, to understand basic numerical information. The problem is aggravated when it comes to evaluating the benefits and harms of treatment options or to understanding test outcomes, which is a severe obstacle to an informed risk management strategy.

Statistical illiteracy reflects not just a lack of education but often results from non-transparent framing of information that may be unintentional, but can also be a deliberate effort to manipulate people. Non-transparent framing of information seems to be the rule rather than the exception in health care: Patients have difficulties finding reliable and comprehensible information, be it online, in brochures on screening procedures, medical pamphlets, or media reports.

Yet all these obstacles do not imply that nothing can be done. The most important mean of improvement consists in teaching the public statistical thinking, combined with training health care workers and journalists in transparent framing. Knowing what questions to ask, which information is missing, and how to translate non-transparent statistics into transparent ones can enable informed risk management strategies. More generally, a better understanding of risks will allow citizens to develop a more relaxed attitude towards health and render the hopes and anxieties of an informed society less manipulable.

Poster Presentations

P 001

Oncogeriatry, a French Experience

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Introduction: Cancer is mostly a disease of the elderly. This population is particularly at risk of adverse drug reactions (ADRs) and should be closely

monitored to lead to a better prevention and management of this iatrogenia.

Aim: To characterize the profile of ADRs of chemotherapy in patients older than 65 years.

Methods: A retrospective study was conducted at the Regional Pharmacovigilance Centre (CRPV) between August 2013 and August 2014.

All the spontaneous or stimulated reporting of ADRs experimented by patient older than 65 years and occurred with antineoplastic therapy were analysed.

Results: A total of 156 patients experimented adverse events under antineoplastics from which 72 have 65 or more than 65 years. The mean age of onset was 71.9 years (65, 87), younger than 75 years and females were predominant (respectively 69.4 % and 54.2 %). The most common cancers diagnosed were breast cancer (12.5 %), colorectal cancer (12.5 %), followed by ovarian cancer (8 %) and vesical cancer (5.5 %). Most of the patients (97 %) were treated with chemotherapy only, a few (3 %) were treated with radiotherapy in addition to chemotherapy, 4 % have metastasis. Hepatic, renal or cardiovascular comorbidities were specified in only 20 % cases.

One hundred and thirty five ADRs were recorded. Most common ADRs were thrombopenia (8 %), allergic reaction (5 %), diarrhoea (4.4 %) and neutropenia (4 %).

The most affected system organ class were blood (24 %), gastrointestinal (12 %), general (10 %), and respiratory disorders (8 %). Neurological (7.4 %), skin (6 %) and cardiac disorders (6 %) were also significant.

90.3 % of the notifications referred to serious adverse drug reactions (n = 55) : 76.4 % with hospitalisation or prolongation of hospitalisation, 6.9 % with an impairment of vital prognosis, 5.6 % with death and 1.4 % of other serious medical conditions. In 11 % of cases, there is a rechallenge including 7 % of positive rechallenge.19 % of ADR referred to platinum chemotherapies, 18 % to pyrimidine analogues, 12 % to monoclonal antibodies and 10 % to tyrosine kinase inhibitors. The most frequent medications involved in ADRs were fluorouracil (n = 8), rituximab (n = 7), oxaliplatine (n = 7), carboplatine (n = 7) and cisplatine (n = 7).

Conclusions: ADRs are most important causes of morbidity and mortality especially in the elderly treated by antineoplastics. Elderly patients suffer also from several comorbidities which must be taken into account rather than the patient chronological age. Traditional chemotherapies are often suspected but targeted therapies are also well involved. By careful ADR monitoring in real life, their incidence could be decreased and their management improved.

P 002

Direct Oral Anticoagulant Bleedings: Patient Profile

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Introduction: Direct oral anticoagulant (DOA) therapies have recently been introduced. Many prescribers use them replacing vitamin K antagonists.

Aim: To describe serious bleeding with direct oral anticoagulant therapies.

Methods: A prospective study was conducted from October 2012 to July 2014 in a French region (1 3 M inhabitants). All the spontaneous or stimulated reporting of serious bleeding adverse drug reactions (ADRs) occurred with dabigatran, rivaroxaban and apixaban were analysed.

Results: 60 patients with bleeding related to DOA were registered. 53 patients (89 %) experimented serious bleedings from which 71.7 % have more than 75 years. The mean age of onset was 78.5 years (39, 93). The mean weight was 72.2 kg (39, 132) with 6 % of weight lower than 50 kg and 6 % of body mass index lower than18.5 kg/m^2. Males were predominant (60 %).

Seriousness criteria included mostly hospitalization (62.3 %), death (17 %) and impairment of vital prognosis (17 %).

Multimorbidity was mostly observed (64.2 %) with at least two chronic diseases. Chronic renal failure was present in 6 % of patients. Risk factors, denutrition, trauma, anticoagulation switch, chronic alcoholism, were mentioned in 64 % of cases.

Bleedings were mainly observed with rivaroxaban (62.3 %), then dabigatran (35.8 %) and apixaban (1.9 %).

Non-valvular atrial fibrillation, prevention of stroke and systemic embolism were the main indications (87 %). Off label use was detected in 24 % of cases (transient ischemic attack indication, interactions).

For the indication of non-valvular atrial fibrillation, 100 % of patients had a CHAD2DS2-VASc score $\geq$2 (mean score = 3.9) and 6 % $\geq$3.

DOA was an initial prescription for 43 % patients, a Vitamin K antagonist switch in 49 % and a fondaparinux switch in 4 %. The Vitamin K antagonist switch was not medically justified in 28 %.

Drug interactions were observed in 43 % of cases. 19 % concerned drugs which can decrease the kidney function and 14 % concerned amiodarone, serotonin antagonist reuptake inhibitor and antiplatelet agents or anticoagulant.

Gastrointestinal (41.5 %) and cerebrovascular bleedings (32.1 %) were the most notified ADRs. 64.2 % of the patients had a renal impairment, including 7 % with serious kidney failure. 26.4 % had a denutrition.

Conclusions: Serious gastrointestinal and cerebrovascular ADRs are significant with DAO. Off label use should be avoided particularly in patients with bleeding risk factors and frailty. The recommendations should be apply to minimize the ADRs. New investigations are needed to determinate the appropriate fondaparinux/DOA switch conditions.

P 003

Current State of Voluntary Drug Intoxications

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Introduction: Few studies have investigated in pharmacovigilance database the suicidal attempt by drugs. This concern is responsible of an important morbidity in the general population.

Aim: To describe the population, drugs involved, adverse effects and seriousness of voluntary drug intoxications.

Methods: A retrospective study was conducted at the Regional Pharmacovigilance Centre between January and April 2015. All the reporting of voluntary drug overdose registered in the database were analysed.

Results: Among the 666 reports recorded over this period, 93 voluntary drug intoxications were collected (14 %). The study population was predominantly female (69.9 % or 65/93). The average age was 38.9 years old with extreme values ranging from 12 to 92 years old. Psychiatric history and history of voluntary drug intoxications were important. Suicidal attempt history was specified in 41 % of those cases. The drugs involved were mostly drug nervous system according to the Anatomical Therapeutic Chemical Classification System (anxiolytics, antidepressants, analgesics…). One death and ten life-threatening situations were observed.

Conclusion: The retrieved data were similar to literature. The repeated voluntary drug intoxications should lead to an increase in vigilance by the health professionals in the psychiatric monitoring and treatments potentially dangerous prescription.

P 004

Prevalence and Potential Risks from Psychoactive Substances and Analgesics in Counterfeit Products

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Introduction: Drug counterfeit affects patients health and poses risks to the public [1]. Counterfeit and unregistered products might contain psychoactive substances with abuse potential. Consequently monitoring centrally active ingredients in counterfeit products is crucial [2].
Aim: This study determined prevalence of psychoactive substances and analgesics in suspected medications and herbs purchased through unauthorised shops and assessed potential side effects.
Methods: 313 samples were collected via inspection or referred by patients (10/2003–12/2014). Detection of active ingredients including psychoactive substances and analgesics were performed in Drug Laboratory, MoH, UAE. Adverse Drug Reactions (ADRs) were monitored by patients voluntary reporting.
Results: 84/313(26.8 %) of products contained centrally active ingredients and analgesics. 79 products contained single ingredient while 5 products contained two ingredients . The most common ingredient was Sibutramine 55/84(65.5 %), followed by analgesics 17/84(20.2 %) and other centrally active agents 17/84(20.2 %). Combined ingredients included (sibutramine, caffeine), (sibutramine, Fluoxetine), (Acetaminophen, Piroxicam), (Piroxicam, paracetamol) and (Tramadol, Meloxicam).

Table 1 Percentage of single active ingredients found in the products

CNS ingredient (%)	Analgesics (%)
Sibutramine, 53 (63.1)	Salicylic acid, 5 (5.6)
Caffeine, 7 (8.3)	Paracetamol, 2 (2.4)
Fluoxetine, 3 (3.6)	Salicylamide, 2 (2.4)
Nicotine, 2 (2.4)	Piroxicam, 1 (1.2)
Diazepam, 1 (1.2)	Meloxicam, 1 (1.2)
Alcohol, 1 (1.2)	
Amitriptyline, 1 (1.2)	

53/84(63.1 %) of products showed manufacturer name, 60/84(71.4 %) details of country of origin, 42/84(50 %) batch number while 11/84(13.1 %) contained neither label nor trade name. ADRs were evaluated from 3 patients taking products contained sibutramine. Two patients reported increased heart rate and high blood pressure while 1 patient reported constipation and headache.

Discussion: Drug counterfeit remains a potential challenge. Many products might contain centrally active substances without mentioning the ingredients. Counterfeit products sold in illegal shops or herbal chains not supervised by health care professionals don't meet quality standards. Adulteration of products could lead to serious events such as tachycardia and hypertension. The current study didn't show significant prevalence of drugs of abuse which could be due to high degree of control by drug enforcement department.
Conclusion: Effective Pharmacovigilance and medication safety programs can reduce counterfeit risk. Pharmacovigilance authorities can benefit from cooperation with Drug enforcement agencies in evaluating prevalence of psychoactive substances [3].
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P 005

The Comparative Risk of All-Cause Mortality in Older Patients Prescribed Opioids for Non-Malignant Pain: A Retrospective Observational Cohort Study

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Introduction: Opioids are indicated for the treatment of acute moderate to severe pain and also have an established role in pain management associated with cancer and palliative care [1]. There has been a trend towards use of these drugs in treating non-malignant chronic pain despite the risk of increasing tolerance and dependence [2]. Previous studies suggest variation in adverse event rates between the different opioids, particularly the risk of all-cause mortality [3].
Aim: To compare the risk of all-cause mortality in adults aged 65+ years prescribed alternative opioids for non-malignant pain in UK primary care.
Methods: Anonymised data on patients newly prescribed an opioid 1990–2012 were extracted from the Clinical Practice Research Datalink. Patients with a previous record of an opioid or NSAID prescription, history of malignancy, opioid dependence or illicit drug use in the 365 days prior to the index date were excluded. Follow-up was censored upon transfer out of the GP practice, last data collection date, date of switch to a different opioid, gap in treatment of more than 90 days, 365 days after the final opioid prescription, death or 31st December 2012, whichever was earliest. Kaplan–Meier curves and the Wilcoxon test were used to test the equality of survival functions for the most commonly used opioids due to evidence of non-proportionality.
Results: 207,765 patients were newly prescribed an opioid with 31,188 deaths during a median follow-up of 1.08 years. 39.2 % of patients were male and the mean (SD) age at first prescription was 75.9 years (8.6). The most frequently prescribed opioids were tramadol (35.5 %), codeine (31.8 %) and dihydrocodeine (13.4 %). Survival for buprenorphine, diamorphine, fentanyl, and morphine was significantly consistently lower

relative to codeine ($p < 0.0001$), tramadol showed significantly consistently higher ($p < 0.0001$) survival. The survival curve for dihydrocodeine was similar to, but repeatedly crossed that of, codeine.

Conclusions: Risk of all-cause mortality varies among the most common different opioids when used among older adults for non-malignant pain. Confounding by indication likely explains this. The initial finding of a decreased risk of all-cause mortality with tramadol compared to codeine is interesting and warrants further consideration, adjusting for confounding and accounting for non-proportional hazards. As tramadol is more potent than codeine [4], we would expect it to be used to treat more severe pain. Cause-specific mortality will also be assessed through linkage with Office for National Statistics death registration data.

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P 006

Optimising Methods for Collecting Participant-Reported Safety Endpoints in Antimalarial Drug Clinical Research

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Introduction: Sub-optimal safety evaluation methods negatively affect individual drug studies, while disparate methods between studies impede data synthesis. The best practices for questioning participants to obtain subjective adverse event (AE), medical history and non-study medication reports in clinical research are unclear, yet methodology research reveals that the type of questioning can influence the data detected. A global survey shows that anti-malarial drug clinical researchers use various questioning methods to obtain these reports.

Aim: To facilitate consensus among anti-malarial drug clinical researchers about optimal methods for collecting participant-reported safety data.

Method: A systematic review was undertaken of research comparing methods for questioning participants about AEs in clinical trials. Anti-malarial researchers were also invited to take part in a Delphi study about the design of relevant, important and feasible questioning methods to obtain participant-reports of AEs and non-study medication; they were provided with a literature summary and asked to anonymously rate various questioning methods, then presented with group responses and asked if they would like to amend their own ratings.

Results: The systematic review revealed over 30 studies demonstrating that more detailed questioning increases the sensitivity of AE detection. However, the impact of different questioning methods on the nature of AEs detected is unclear. A preliminary analysis of the Delphi shows that consensus was achieved for potentially using the following methods for eliciting subjective AEs: a general question concept; structured questions about symptoms; use of mobile phones, diaries, visual analogue scales and photographs of symptoms; openly engaging with participants. For eliciting reports of non-study medication use, consensus was achieved for using: a general question concept; structured questions about medicine sources, treatment classes and indications, and asking about local treatments by name; showing photographs, drawings or samples of commonly used treatments; asking participants to bring non-study medication to visits.

Conclusions: It is important to find methods for questioning clinical research participants about their health and non-study medicines that elicit accurate data, as these reports underpin subsequent steps when representing an experience as an eventual safety end point. We facilitated a conversation with antimalarial drug researchers about these issues and have drafted a menu of question options for future collaborative methodological research. This should contribute to developing a framework for researchers to use when planning globally-relevant, yet context-specific, safety data collection strategies.

P 007

Compliance with Legal Requirements at Community Pharmacies in Saudi Arabia

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Background: Uncontrolled dispensing of medicines through community pharmacies is extensively documented as a problem in most of the developing countries.

Objective: To assess community pharmacy compliance with dispensing regulations that prohibits the dispensing of restricted medications in the absence of a physician prescription.

Method: A cross sectional study conducted in the period between October 2014 and January 2015. The researchers have selected 10 prescription only medicines and have randomly visited different community pharmacies across six major provinces in Saudi Arabia. The researchers requested to purchase these medications in the absence of physician prescriptions. Descriptive statistics were produced for all survey items. Descriptive statistics were used to report responses using Statistical Analyses Software (SAS 9.3). A chi-square test or Fisher exact tests were used to analyze the categorical data. All statistical tests were conducted with a 2-tailed alpha of 0.05.

Results: A total of 150 community pharmacies have been visited during the study period. Out of 10 requested drugs, all classified as prescription only medications, only 2 drugs namely enoxaparin and codeine were rejected to be dispensed without a prescription in two pharmacies only. The most frequently dispensed medications were Isosorbide dinitrate (81 %), nitroglycerin (77 %) and verapamil (67 %), while the less frequent were ciprofloxacin, propranolol and methyldopa. The rest of the requested drugs were dispensed by more than 70 % of the visited pharmacies, indicating a high level of non-compliance with the regulations. Geographically, Western region pharmacies have less compliance (10 %) compare with other regions (40 %), ($p = 0.01$).

Conclusions: Pharmaceutical malpractice remains a major threat to community health. The vast majority of pharmacists are violating the law

of practice and thus neglecting the harms that such practices would cause to the community.

P 008

Completeness of Medications Prescriptions: Prescription Errors Study in Hail Region (PeSHR)

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Background: Medication errors can occur during any of the medical treatment phases that begin with diagnosis and finishes with drug dispensing. Prescription errors is a commonly occurring error that can lead to multiple errors potentially placing patient lives in jeopardy.
Objective: The current study aims at identifying the types and frequency of prescription errors in a referral tertiary hospital in Hail city, the regions' largest hospital.
Method: A retrospective cross sectional analysis of physician prescriptions that were issued over a one month period (Oct–Nov 2014). Researchers have randomly selected and reviewed 1000 written prescriptions from different departments (Outpatients clinics and ER) for any potential errors as per Neville's classification. Prescription errors were classified as major (potentially life threatening), minor (non-life threatening) or trivial.
Results: While the majority of the reviewed prescriptions have at least one error, alarmingly 8 out of the 1000 reviewed prescriptions had no patient name or file number. Amongst other errors, patient file numbers and medication dosages were missing in more than 20 and 40 %, respectively. At least 30 % of the reviewed prescriptions were deemed to have had illegible handwriting, which requires pharmacist judgment to decipher the writing. Non-life threatening items including age, physician signature and stamp, date, sex diagnosis and weight were missing in more than 50 %, with the later was missing from all transcripts. Prescriptions wrote by ER physicians had more missing items compared to those wrote by outpatients clinics ($p = 0.01$).
Conclusion: While avoidable errors will continue to occur for many different reasons, an urgent need for a system to force prescribers to write all prescription items.

P 009

Notification Systems Allowing Marketing Authorisation Holders to Inform Competent Authorities About New Information Related to Their Medicinal Products

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Marketing Authorisation Holders (MAHs) shall continuously monitor the safety, quality and efficacy of their medicinal products. When new information impacting on the benefit/risk of the product arises, MAHs shall forthwith inform CAs so that adequate measures to minimise and communicate the risks can be taken. In the EU, notification systems have been established based on the nature of the information that shall be communicated and stakeholders that shall be informed on time whilst avoiding duplications (e.g. Emerging Safety Issues, Quality Defects, and Withdrawn Products Notifications).
This presentation aims at describing the notification systems allowing MAHs to inform Competent Authorities (CAs) about new information emerging on their medicinal products. Upon receipt, the EMA quantifies and qualifies such information which contributes to the protection of public health through adequate assessment and decision making on appropriate risk minimisation measures. The audience will be provided with figures on the number of notifications received, taking into account the type of authorisations in the EU of the products concerned, the (regulatory) procedures that have been used to further evaluate the information, and subsequently the (regulatory) measures that have been taken to promote and protect public health (e.g. update to the product information, suspension, revocation of the products).

P 010

Revision of Guidance on Screening for Adverse Drug Reactions in EudraVigilance

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Introduction: Knowledge arising from the IMI PROTECT project and the proposed widening of EudraVigilance access to include Marketing Authorisation Holders have caused the European Medicines Agency (EMA) to review guidance on the way quantitative and other rule based signal detection methods are implemented.
Aim: To explain the evidence behind revision of the guidance aimed at improving the efficiency of routine signal detection using EudraVigilance.
Methods: PROTECT investigated a number of disproportionality measures, strategies for subgrouping the datasets and various decision rules for defining a signal of disproportionate reporting (SDR). These were further evaluated for sensitivity and precision in routine statistical signal detection in EudraVigilance.
In addition to statistical rules, a comprehensive and efficient routine signal detection system seeks to integrate a number of different methods to prioritise drug-event associations for evaluation. Development of these additional methods has focused on the creation of a list of Designated Medical Events (DME) that should be reviewed independently of statistical criteria of disproportionality.
Integrating the empirical information from PROTECT with the other methods creates the challenge to obtain gains in signal detection efficiency while respecting clinical priorities. To support this aim, the EMA, supported by the Pharmacovigilance Risk Assessment Committee, is revising the guidance on signal detection in EudraVigilance in a stepwise fashion incorporating a pilot of the recommendations to allow further evaluation and improvements if needed.
Results: The recommendations being considered for implementation into guidance include a change from PRR to ROR and a calculation based on limited stratification of the data, primarily by geographical region. A decline in precision over the life-time of a drug suggests that SDR thresholds should be varied for drugs with established safety profiles. A quarter of confirmed signals in 2013 were related to DME PTs; of these 17

were raised by screening EudraVigilance and 9 (53 %) did not have SDR confirming the utility of this safety net. The DME list has been refined on the basis of experience gained. Results from the piloting of the ROR, stratification and new thresholds will be presented.
Conclusion: Recommended changes have the potential to allow more signals to be detected without increasing workload. Implementation in business processes and through revised guidance is being preceded by a prospective pilot phase in real-world signal detection and, to gather further evidence of the expected benefits, a protocol to study the changes in efficiency over time is being developed. This methodology will form the basis of future quality assurance.

P 011

Drugs Withdrawn for Hepatotoxicity from the EU and US Market Since 1997. What Information Could be Useful?

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Background: From 1975 to 2007, on 47 drugs withdrawn over the world, one third has involved hepatotoxicity [1, 2].
Previous studies figured out the type of evidences used to support the withdrawal of products which is mainly spontaneous reports. However, no study has analysed the available information during drug development. Did we learn from experience to improve liver toxicity predictivity?
Aim: The aim of the study is to explore and compare information provided from the development of the drugs to its launching since 1997 in Europe or in USA.
Methodology: We selected drugs withdrawn for hepatotoxicity from 1997 to 2012 in Europe and/or in USA either by a marketing authorization holder or by drugs agency. The withdrawal decision was identified from a search within the EMA and FDA websites and PubMed. After summarizing the trials, mechanism and term of occurrence of liver injury of the drugs, we analysed information provided on drug safety.
Results: In the European Union and in USA, 8 drugs, announced as a therapeutic breakthrough and commercialized quickly, were withdrawn for liver toxicity reasons from 1997 to 2012: tolcapone, troglitazone, trovafloxacin, bromfenac, nefazodone, ximelagatran, lumiracoxib and sitaxentan2. All the drugs have shown liver abnormalities during clinical trials while the preclinical studies were unable to detect liver injury. Bromfenac and ximelagatran have both been withdrawn because liver injury occurred after a longer duration of treatment not studied in early clinical trials. The unexpected occurrence of liver injury was and still is one of the reasons to stop marketing because delay of onset is significant or liver monitoring was useless.
Discussion/conclusion: Over the years, the animal's predictive values for DILI have not been improved and clinical trials are still poorly informative regarding this issue, thus post-marketing monitoring is still mainly used to identify potential rare cases of hepatotoxicity.
Delayed reactions still remain difficult to assess and to manage and severity of liver injury cannot be predicted by ALT increase alone because rare events may be missed. Although DILI remains largely unpredictable, many tools that contribute to a better risk management have been developed however there is yet no example of an efficient prevention system.

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P 012

Liver Transplantation for Drug Fulminant Hepatitis in France

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Background: Drug induced liver injury can result in serious clinical outcomes including fulminant hepatitis (FH) and the need for liver transplantation. [1] Few data were published on FH caused by drugs and leading to liver transplantation. [2] From the national registry of biomedicine agency, we identified and assessed drugs involved in FH and leading to liver transplantation over 12 years in France.
Aim: From the national registry of biomedicine agency, we identified and assessed drugs involved in FH and leading to liver transplantation over 12 years in France.
Method: From the national biomedicine agency file, a query was made on liver transplants for fulminant hepatitis in France from 1998 to 2010. Data have been submitted to French pharmacovigilance centres to approach the transplant centres to identify the etiology of fulminant hepatitis.
Results: Over the study period, 563 FH leading to liver transplantation were registered and 405 were analysed. Among them, 126 FH induced by drugs were identified. More than the half was caused by acetaminophen at therapeutic dose or overdose.
NSAIDs (ketoprofen, nimesulide, diclofenac, ibuprofen, flurbiprofen) are involved in 13 % of drug FH and are associated in 70 % of cases with other drugs (mostly acetaminophen.)
Anti-tuberculosis drugs (isoniazid and/or rifampicin and/or pirazinamide and/or myambutol) are involved in almost 10 % of drug fulminant hepatitis.
Discussion/conclusion: More than a third of FH leading to transplantation have a drug etiology. Therefore, drugs are the leading cause of liver transplantation for FH. Half of fulminant hepatitis analysed relate overdose and drug most frequently involved in the occurrence of FH is acetaminophen followed by NSAIDs and anti-tuberculosis. However, although TB require regular monitoring of transaminases, the occurrence of fulminant hepatitis remains important in this drug class. These drugs induced HF incidences are probably underestimated because several cases of liver transplants suggest a drug involvement but identification of the molecule had not been possible. Moreover, these results are preliminary and could be changed if more FH leading to liver transplantation are analysed.
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P 013

DILI and Diagnosis Tools Improvements

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Background: Drug Induced Liver Injury (DILI) events are the main cause of regulatory action including denial of marketing approval, restrictions with respect to clinical indications, and withdrawal from the marketplace. [1] Although DILI is unpredictable, many tools that contribute to a better risk management have been developed but improvements are still needed in their interpretations.
Aim: To present the potential evolving diagnosis modalities on DILI
Methodology: A Pubmed literature review has been performed using the terms 'drug induced liver injury', 'diagnosis', 'toxicogenomics', 'proteomics' and 'pharmacogenetics'.
Results: We identify 5 main topics which can contribute to the improvement of DILI diagnosis the next years:

1. The genetic studies using next generation sequencing. DILI has been linked to specific genetic associations and the genetic variability of the HLA system is the single most important risk factor for it.
2. The use of high-dimensional biology in research area such as proteomics, transcriptomics, metabolomics, genomics.
3. New signal detection tools for pharmacoepidemiological studies. The uses of natural language processing algorithms, which can search for key words in a text field such as "hepatotoxicity", have demonstrated an improved sensitivity and specificity for DILI [2].
4. Collaboration between different networks of DILI via a worldwide consortium could integrate countries like Europe but also India, China.
5. The creation of Biobanks from mechanistic studies can lead to the improvement of diagnoses and classification of DILI according to the patient's molecular profile at several levels of exposure such as genome, environment and lifestyle. CK18 and miRNA-122 were evaluated as superior biomarkers compared to ALT in terms of sensitivity and specificity in DILI [3].

Conclusion: Approaches in the development of more reliable tools of DILI are needed.
Proteomics, genomics, biobank, international networks, signal detection tools and pharmacoepidemiological studies may allow the discovery of clinical biomarkers for early detection of liver toxicity. These technologies can provide added selectivity and sensitivity in preclinical drug safety testing.
However, diagnosis tools improvements for DILI are currently under investigation in various mechanistic and pre-clinical models and also in large clinical trials.

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P 014

Detection of Drug-Induced Hydro-Electrolytic Adverse Reactions by Retrospective Analysis of Renal and Metabolic Physiological Investigations Data

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Introduction: Several drugs can induce hydro-electrolytic Adverse Drug Reactions (ADRs). Despite their seriousness, these ADRs remain often under-reported. Our previous research showed interest of laboratory data to improve the collection of ADRs [1].
Aim: The aim of our study was to identify cases of drug-induced hydro-electrolytic disorders from analysis of renal and metabolic physiological investigations.
Material and Methods: A retrospective study was performed in the Department of Renal Physiological Investigations in the Toulouse University Hospital (South West of France) Medical records were collected from 1 January 2012 to 30 June 2014. All cases involving a drug as the potential origin of the hydro-electrolytic disorder were analysed. Data concerning patients (age, gender), drugs and ADRs outcome were collected.
Results: A total of 2147 patients (855 in 2012, 837 in 2013 and 455 in the first semester of 2014) were investigated. In 19 cases [0.9 %, 7 in 2012 (0.8 %), 6 in 2013 (0.8 %) and 6 in the first semester of 2014 (1.5 %)], a drug was suspected. Mean age of patients was 60.0 ± 29.0 (63 % males). Previous medical history was: arterial hypertension (n = 8), diabetes (n = 4). The table summarizes the cases and the drugs involved. Outcome was favourable: 12 cases after withdrawal of suspected drug, 1 case spontaneously resolved. Outcome was unknown in 5 another cases. In 2 cases, ADRs persisted due to the continuation of the suspected drugs. Only, 1 case of ADRs was spontaneously reported to the Center of Pharmacovigilance (under-reporting rate = 95 %)

Table Description of the cases of drug-induced hydro-electrolytic disorders

	Drugs	Number of cases
Hypomagnesemia	Esomeprazole pantoprazole	4
Metabolic acidosis	Zonisamide topiramate	2
Hyponatremia	Oxacarbazépine eslicarbazépine	2
Hyperkaliemia	Irbésartan	1
Urinary lithiasis	Atazanavir topiramate	4
Tubulopathy	Indinavir ifosfamide tenofovir cisplatine/carboplatine	8

Conclusion: Our results suggest that hydro-electrolytic disorders requiring physiological investigations are explained by drugs in 1 out of 100 patients. The rate of under-reporting is high. According to our previous

studies, these data confirm that laboratory data analysis could be an interesting tool to detect some serious ADRs.

Reference

1. Noize et al. Life threatening drug-associated hyperkaliemia: a retrospective study from laboratory signals. Pharmacoepidemiol Drug safe. 2011;20:747–53.

P 015

Hospital Admission due to Bleeding or Thromboembolic Events in Patients with Atrial Fibrillation: Direct Anticoagulant Versus Vitamin K Antagonists

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Introduction: Atrial Fibrillation (AF) is the most frequent heart disease requiring anticoagulation. Two types of oral anticoagulants are currently available: Vitamin K Antagonists (VKA), and Direct Oral Anticoagulants (DOA), more recently approved.

Aim: First, to compare the characteristics of events (bleeding or thromboembolic) leading to hospitalization in patients exposed to DOA for AF to those exposed to VKA. Second, to describe the profile of patient exposed to DOA.

Methods: Retrospective monocentric cohort study. Study population was patients with AF, hospitalized in Toulouse University Hospital for bleeding or thrombotic events between 1st January and 31st December 2013 and exposed DOA or VKA for AF. Data source was the French hospital discharge database provided by the Hospital Department of Medical Information. "Bleeding events" and "Atrial Fibrillation" ICD-10 diagnoses codes were crossed. Accuracy of chronology and anticoagulant exposure were assessed by analysis of medical records. A regression logistic model was performed to compare the characteristics of events (adjusted on potential confounders) and describe factors associated to DOA prescription.

Results: Patients characteristics and main events are summarized in the table.

Table Patients characteristics and main events

	Bleeding events N = 385 (55 DOA and 330 VKA)	Thromboembolic events N = 201 (28 DOA and 173 VKA)
Patients characteristics, n (%)		
Age, mean (std)	79.8 (9.6)	79.4 (10.1)
Death	31 (8.1)	23 (11.4)
with potential contribution of the drug	24 (6.2)	19 (9.5)
Renal insufficiency	91 (23.6)	50 (24.9)
History of bleeding	182 (47.3)	32 (15.9)
Type of event, n (%)		
Cerebral bleeding	162 (42.1)	
DOA	24 (43.6)	
VKA	138 (1.8)	
Gastrointestinal bleeding	62 (16.1)	
DOA	9 (16.4)	
VKA	53 (16.1)	
Stroke		137 (68.2)
DOA		22 (78.6)
VKA		115 (66.5)
Peripheral arterial thrombosis		23 (11.4)
DOA		2 (7.1)
VKA		21 (12.1)
Myocardial infarction		32 (15.9)
DOA		4 (14.3)
VKA		28 (16.2)

Bleeding events. Patients treated with AntiPlatelet Agents (APA) were mainly in the VKA group ($p = 0.04$). There was no significant difference for mortality or localization of bleeding events between groups. The only factor associated with DOA prescription was cardiopathy ($p = 0.006$).

Thrombotic events. VKA patients were older ($p = 0.004$). There was no significant difference for mortality or localization of thrombotic events between groups. Factors associated with DOA prescription were age ($p = 0.003$) and concomitant APA prescription ($p = 0.045$).

Conclusion: Our data did not found evidence for difference of localization, frequency and mortality of bleeding or thrombotic events leading to hospitalization in patients exposed to DOA or VKA. These data obtained in real life clearly differ from those obtained in clinical trials performed during drug development.

P 016

Hospital Admission due to Bleeding in Patients with Atrial Fibrillation: Antiplatelet Agents or Oral Anticoagulants?

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Introduction: Atrial Fibrillation (AF) is the most frequent heart chronic arrhythmia. Anticoagulation is recommended to prevent thromboembolic risk in patients having at least one thromboembolic risk factor. However,

due to inconvenience of use of Oral AntiCoagulant (OAC) and their risk of bleeding in patients with several comorbidities, antiplatelet agents (APA) remain used in this indication, despite recommendations.

Aim: To compare the characteristics of bleeding event leading to hospitalization in patients exposed to APA for AF to those exposed to OAC. Second, to Second, to describe the profile of patients receiving APA.

Methods: Retrospective monocentric cohort study. Study population was patients with AF, hospitalized in Toulouse University Hospital for bleeding events between 01/01/2013 and 31/12/2013. Were included patients exposed to APA or OAC for AF. Data source was the French hospital discharge database provided by the Hospital Department of Medical Information. "Bleeding event" and "Atrial Fibrillation" ICD-10 diagnoses codes were crossed. Accuracy of chronology and drug exposure were assessed by analysis of medical records. A regression logistic model was performed to compare the type of bleeding event, adjusting on potential confounders. Another one was performed to describe factors associated to APA prescription. Analyses were performed using SAS® 9.4.

Results: A total of 368 patients were included: 67 were exposed to APA and 301 to OAC (49 Direct Oral Anticoagulants, 252 Vitamin K Antagonists). Mean age was 79.8 ± 9.8 years and sex ratio 1.1. A total of 29 patients (7.9 %) died with a potential contribution of APA or OAC in 23 cases. There was no difference in mortality between groups. Patients treated with APA were older ($p = 0.047$). CHA2DS2-VASc and HAS-BLED scores were not different between both groups. Nearly 25 % of the patients had renal insufficiency. More than 50 % had history of bleeding and almost 20 % received other drugs that might increase the risk of bleeding. Cerebral bleeding was found in 97 patients (26.4 %) and gastrointestinal bleeding in 54 (14.7 %). No significant difference was found between groups in terms of bleeding events. Factors associated with APA prescription were age [OR 1.03 IC95 % (1.00–1.06), $p = 0.004$] and history of myocardial infarction (5.00 [2.38–11.11], $p < 0.001$).

Conclusion: No difference was found between groups in terms of type of bleeding events or fatal outcome. Then, these results confirm data of the literature about the absence of favourable benefit/risk of APA alone in AF.

P 017

Do We Need Pharmacovigilance Education and Do Adolescents Have Adequate Knowledge Regarding Proper Medicine Use?

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Introduction: Studies about adolescents' medicine use are quite rare in comparison with adolescents' alcohol, tobacco and illicit drug use. However, more and more teenagers use different kinds of over-the-counter (OTC) drugs or other prescribed drugs every day. Adolescents are vulnerable population from the viewpoint of potential misuse of medications. The knowledge about medicines and medicine use is essential to avoid risky administration of drugs which could lead to health problems, hospital admissions or adverse events. Psychosomatic symptomatology also could be real danger for unintentional and intentional product misuse or medication errors.

Aim: The current study was conducted to provide baseline data about Hungarian teenagers' knowledge, attitude and practice about OTC drugs, prescribed medications and other substances use.

Method: Our sample consisted of 387 pupils from elementary schools (Grade 7–8). The study was performed in Bekes county in Hungary involved seven small towns and villages. Self-administered questionnaires were applied that measured sociodemographics variables, psychosomatic symptoms, beliefs and attitudes related to substance use and knowledge about medicine use. Descriptive statistics, cross tabulations and chi square test were used to test these relationships with SPSS MS 19.0 statistical program.

Results: We could identify several fields where pupils' knowledge is insufficient. We gained information about the pattern of medicine use among teenagers and the characteristics of psychosomatic symptoms and medical problems in this age group. In case of adolescents' knowledge about medicine and psychosomatic symptomatology we could identify subpopulations at high risk for misuse of pharmaceutical products.

Conclusions: During health promotion and prevention programs we should pay attention to adolescents' legal and illegal drug use, especially in terms of knowledge about of these substances. It could suggest the need for government-sponsored or industry-sponsored education efforts regarding correct use of medicines. The better knowledge in younger ages could improve the awareness of medicinal product use in adulthood.

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P 018

Characterising ADRs as Continuous or Binary Variables: Principles and Consequences for Terminologies, Labelling, Causality and Risk Assessment and Signal Detection

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Introduction: ADR terms as listed in reference lists often do not seem to adequately allow for the type of variation of these effects and therefore are not immediately applicable for signal detection, product labelling or risk assessment.

Aim: To detect and specify those deficits in reference lists and to suggest improvements which enhance their usability.

Methods: (1) Analysis of how MedDRA and the Common Terminology Criteria for Adverse Events (CTCAE) compiled by the US National Cancer Institute and selected 'ICSRs' take into account the type of variation, i.e. continuous or discrete/binary, of different ADRs. (2) Assessment of how ADR classification by type of variation would impact on causality, harm and risk assessment as well as signal detection and labelling.

Results: MedDRA usually does not provide severity-graded ADR terms, not even if, due to variability of the 'intrinsic' harmfulness of the causative medicine or differences between different drugs, their severity or absolute seriousness can assume a range of different levels and thus are continuous variables ('cADRs'). Examples are myopathy, hypertension and increased levels of transaminases. These terms seem to imply that the ADR severity exceeded a certain threshold or that it was sufficiently characterised by a diagnosis.

CTCAE, on the contrary, usually grades ADR terms by severity/seriousness even if the ADR could, for regulatory (unlike clinical) drug assessment, be regarded as a binary variable ('bADR'). This grading is often based on criteria like complications or necessary interventions which only remotely correlate with the pharmacologically 'intrinsic' ability of the suspected medicine to cause the ADR. Examples are stroke, leukoencephalopathy and bladder perforation.

Consideration of ADR variation shows: Risk factors increase the severity of 'cADRs' and the likelihood of 'bADRs'. Causation means that a drug caused—or contributed to—the severity of a 'cADR' and the likelihood/frequency of a 'b ADR'. Signals are constituted by increased 'cADR' severity or 'bADR' frequency. Harm due to 'cADRs' is represented by the AUC obtained by plotting ADR numbers vs. severity/seriousness and harm from 'bADRs' by their number times typical severity/seriousness. If 'cADRs' end up as 'bADRs' (first painful osteoporosis, than bone fracture) total harm is the sum of both kinds of harm due to both types of ADRs. For risk assessment harm is related to exposure.

Conclusions: Reference lists for regulatory pharmacovigilance should provide several severity grades for 'cADRs' but only one for 'bADRs'. ADR variation should be considered in causality, harm and risk assessment, labelling and signal detection.

P 019

Pharmacovigilance Education in Pharmaceutical Company—An Example of the Czech Republic and Slovakia Sanofi Affiliate

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Aim: Pharmacovigilance education within pharmaceutical company belongs to essential and mandatory trainings, which all employees of the company should undergo regularly. There are presented, on the example of the Czech Republic and Slovakia Sanofi affiliate, approaches, training plans and tools used for the pharmacovigilance training delivery across the company affiliate, manufacturing site and headquarters. External parties like vendors and subcontractors pharmacovigilance training is also addressed. Last, but not least, cooperation between pharmaceutical companies within pharmaceutical companies association is presented.

P 020

Pharmacovigilance in Undergraduate Medical and Pharmacy Education in Europe

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Introduction: Healthcare professionals have key responsibilities in drug safety monitoring activities and teaching pharmacovigilance in undergraduate medical education is of high importance.

Aim: The aim of this study was to assess pharmacovigilance teaching content in the curricula of medical and pharmacy schools across Europe.

Methods: The survey was conducted from March through May 2015. All the European schools and faculties with medicine and pharmacy undergraduate programmes and with available e-mail contacts to deans and directors of teaching were addressed. The online questionnaire consisted of 25 open-and closed-ended questions and examined the integration of pharmacovigilance teaching into medical and pharmacy programmes, pharmacovigilance course content, depth and approaches to pharmacovigilance teaching and learning. Data were processed using descriptive statistics.

Results: Of the 360 institutions contacted, 119 (33 %) participated in the survey. Pharmacovigilance was strongly visible in all years of medical and pharmacy study, usually incorporated into clinical pharmacology or clinical pharmacy as a compulsory module. A small number (6 %) did not have pharmacovigilance in their curricula. The teaching was mostly (95 %) provided by in-house academic personnel. On average fewer lectures and seminars were addressed in medicine when compared to pharmacy programme. More than half of the respondents (58 %) indicated the necessity of pharmacovigilance subject as a stand-alone course in health-related degree programmes.

Conclusion: There is a positive indication that pharmacovigilance is taught in European medical and pharmacy schools. Although there was considerable variability between medical and pharmacy programmes in coverage and breadth of the subject, the delivered knowledge base will facilitate the skills required at graduation.

P 021

The Role of Pharmacovigilance Centres as Drug Information centre: The Moroccan Experience

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Introduction: The lack of knowledge concerning drugs and rational use of drugs, the huge number of drugs increasing, self-medication and the need for health authorities and assurance companies to have exact information on drug safety, raised the need to have efficient, independent drugs information centres. To this end, Drug information centres were born in hospital universities, in Poison Control Centre and Pharmacovigilance centres in order to provide the adequate needed information for health care professionals (HCP) and the general public.

Aim: To assess the health product information requests received at the Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM) to categorize types of reporter and type of information requested in order to improve patient safety.

Method: It was a retrospective study of the health products information requests database of the CAPM from January, the 1st 2014 to December 31th, 2014, 24 h on 24. We compared the number and the type of information requests received from Health Care Professionals (HCP) and the general public.

Results: The CAPM as drug information centre received 332 requests for health products information from HCP (66 %) and the general public (33 %). HCP and the public have the same type of information requests. Pregnancy and breastfeeding information requests concerned 38.5 % of all requests, followed by questions concerning rational use of drugs as indications, posology and contraindications (22.5 %), adverse drug reactions (6 %) and drug–drug interaction 4.8 %. However, pregnancy and

breastfeeding information requests are seen more with HCP (49 %) than with the general public (9.6 %) and rational use of drug requests are seen more with general public (43.6 %) than with HCP (12.8 %). HCP from health authorities and health assurance requested information concerning regulation and safety profile of drugs (25.0 %).

Conclusion: This study highlighted the importance of having a Drug information centre within a Pharmacovigilance Centre to improve patient safety and to decrease the risk of medication errors due to an irrational use of drugs and to unsafe use of particular drugs during pregnancy and breastfeeding.

Further sources of information/Reference

1. Requirements for Drug Information Centres: http://www.fip.org/files/fip/PI/RequirementsforDrugInformationCentres.pdf

P 022

Pharmacovigilance from a Public Health Point of View—Implications of Reduced Renal Function

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Introduction: Decreased renal function is a well-known source for variability in drug response. It is prevalent, but often overlooked, in the elderly. For drugs dependent on the renal function for their elimination, inappropriate drug dosing may result in pharmacological adverse drug reactions (ADRs) (type A), dose-and concentration dependent, thus predictable and theoretically preventable.

Aim: To determine the renal function in patients hospitalized because of ADRs.

Methods: We reviewed medical records with an ICD diagnosis Y57.9 ("Adverse drug effect in therapeutic use") in two Emergency hospitals in Stockholm: Intermediary Care Unit of Internal Medicine within the Emergency Department. Karolinska University Hospital (50 patients, 1.1 % of all patients) median age 77 (26–94) and Department of Internal Medicine, St Göran Hospital (122 patients, 0.8 %) median age 78 (21–97). These ADRs were judged by eight physicians to be pharmacological (Type A) or idiosyncratic (Type B) reactions.

Elderly patients may have decreased renal function due to physiological changes and due to age-related diseases, e.g. atherosclerosis, heart failure, and diabetes. The clinically used plasma creatinine (P-crea) is unreliable as a measure of renal function, particularly in the elderly. These patients may have reduced muscle mass with P-crea values within the reference range even when creatinine clearance (CLCR) is below 50 mL/min. The renal clearance of drugs is usually correlated to the renal creatinine clearance. We estimated renal function by the most established equation, the Cockcroft Gault (CG) equation, presenting absolute values of creatinine clearance (eCrCl mL/min).

Results: Pharmacological (Type-A) reactions were judged in 74 of 109 women (68 %) and in 46 of 63 (73 %) men. Idiosyncratic (Type-B) reactions were seen in 35 (32 %) women and 17 (27 %) men. Among patients with a Type-A reaction 68 % had eCrCl below 60 mL/min (level of concern for drug treatment). In Type-B reactions only 23 % had a clearance below 60 mL/min. Warfarin, digoxin, oxycontin and trimethoprim were the drugs most frequently causing ADRs. Less than 5 % of these 172 ADRs were reported to the regulatory agency.

Conclusion: Reduced renal function is a common reason for ADRs leading to hospitalizations. These pharmacological (Type-A) ADRs are major public health problems that ought to be of concern for all parties involved: regulatory agencies, drug industry as well as health care providers.

P 023

Risks Associated with a New Fixed-Dose Combination Drug

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Introduction: Combination products are likely to bear the same risks as their single components but the risk perception for these drugs is generally higher due to unpredictable interactions between the active ingredients. Nevertheless, combination products can also have benefits that are greater than the administration of a single active ingredient; therefore the benefit–risk balance of a combination product can be different or similar to that of the single constituents of the combination product itself. Netupitant-palonosetron combination is an oral fixed dose combination with a safety profile comparable to that of its single components recently marketed in the USA, approved in the EU and Australia and close to registration in many countries world-wide. Palonosetron is a serotonin type 3 receptor antagonist (5-HT3 RA) extensively used for the prevention of chemotherapy induced nausea and vomiting since 2003 while netupitant is a neurokinin-1 (NK1) RA 1-2.

Aim: To compare the most important identified and potential risks of the netupitant-palonosetron fixed combination with those of the single active ingredient (palonosetron and netupitant).

Methods: For some potential risks, specific studies were performed for both palonosetron and the combination product. In the netupitant-palonosetron EU RMP, in addition to the risks associated with netupitant, the known palonosetron potential risks were clearly identified and considered adopting a conservative approach.

Results: With both palonosetron and netupitant, the evidence for QT interval prolongation originates from pre-clinical studies while the thorough QT studies in healthy volunteers showed neither signal of any effect on AV conduction or cardiac depolarization nor new clinically relevant morphological changes. Phospholipidosis was considered a potential risk associated with netupitant even though it was only observed in pre-clinical studies. Other risks, such as interactions with other drugs, were specifically attributable to the single active ingredient. No additional risks were generated by the combination of the two constituents.

Conclusions: As for palonosetron, also for netupitant-palonosetron fixed dose combination routine risk minimization measures were considered to be appropriate. No additional risk minimization measures are included in the EU-RMP and REMS was not required by the FDA.

Further sources of information/References

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P 024

Use of the Computerized Hospital Database in Pharmacovigilance: Is It Relevant for the Detection of Drug-Induced Thrombocytopenia?

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Introduction: Underreporting is the main limitation of pharmacovigilance spontaneous reporting system. We aimed to evaluate the performance of a query based on an ICD-10 code in the computerized hospital database (PMSI) to identify drug-induced thrombocytopenia (DIT).
Methods: A retrospective study was conducted over a period of one year (2014) in the University Hospital of Saint-Etienne. Potential DIT cases were extracted from PMSI using the ICD-10: « Secondary thrombocytopenia ». Then, we analysed every hospital medical records and selected those corresponding to DIT. We compared these cases to those reported to the Pharmacovigilance Centre of Saint-Etienne during the same period (cases identified in the French Pharmacovigilance Database using the MedDRA High Level Term « Thrombocytopenia »). We used the capture-recapture method to evaluate and compare the completeness of each source and to estimate the underreporting.
Results: We collected 90 cases of "secondary thrombocytopenia" from the PMSI. After in-depth analysis, we selected 12 cases of DIT. Other aetiologies of thrombocytopenia were mainly cirrhosis, myelodysplasia, disseminated intravascular coagulation or sepsis. In 2014, 16 cases of DIT were reported to the Pharmacovigilance Centre of Saint-Etienne. Only 4 common cases were identified by both sources. The capture-recapture method estimated to 44 the total number of DIT. So, the underreporting was evaluated at 45 %. The completeness of PMSI database and spontaneous pharmacovigilance system was of 27 % and 36 %, respectively. The main drugs involved in the 24 detected cases of DIT were antibiotics and heparins.
Conclusion: In this study, PMSI database allowed to identify cases of DIT not reported to our Pharmacovigilance Centre. However, the ICD-10 code "secondary thrombocytopenia" included too many entities and generated many false positive cases (there is no specific ICD-10 code "Drug-induced thrombocytopenia"). So, the selection of pertinent cases was time consuming. Moreover, the completeness of PMSI database was lower than that of pharmacovigilance spontaneous reporting, contrary to that has been reported in previous comparable studies on other adverse drug reactions. In order to further decrease the underreporting, it could be interesting to use a third data source, such as biological database (for example, the confirmation test for heparin induced thrombocytopenia).

P 025

Before and After the 2013 Alert Concerning Thromboembolic Events with 3rd and 4th Generation Combined Oral Contraceptives: An Impact Study

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Introduction: In light of the recent studies concerning the higher risk of thromboembolic events with 3rd and 4th generation combined oral contraceptives (COCs), the French drug authority expressed its official position in 2013: as first-line treatment, the benefit/risk balance is in favour of 1st and 2nd generation COCs.
Aim: To compare cases of thromboembolic events with COCs or cyproterone acetate (CA) that led to hospitalization at the University Hospital of Saint-Etienne in 2012 and 2014, respectively.
Methods: We performed a retrospective descriptive study for the years 2012 and 2014, which included 15-to 49-year-old women who were hospitalized for pulmonary embolism, cerebral venous thrombosis, ischemic stroke or myocardial infarction and who were exposed to COCs or CA. Cases of interest were identified and selected according to exposure using the computerized hospital database (PMSI) and patients' medical records.
Results: We retained 28 cases in 2012 (average age of 36 years) and 12 cases in 2014 (average age of 31 years). In 2012, 60 % of the cases were venous thromboembolic events (VTE) and40 % were arterial thromboembolic events (ATE). The distribution was reversed in 2014, with more arterial events (58.3 % vs. 41.7 %). Most of the 2012 and 2014 cases occurred with the 2nd generation COCs (46.42 % and 66.6 %, respectively), while the 3rd and 4th generation COCs accounted for 32.14 % (2012) and 8.33 % (2014). Familial history of VTE and age≥40 were the main VTE risk factors while current smoking and age ≥40 were the main ATE risk factors in both 2012 and 2014. A complete recovery was noticed for 60.7 % of the 2012 cases and 92.3 % of the 2014 cases.
Conclusions: The total number of thromboembolic events dropped by 57 % in 2014. The part of 3rd and 4th generation COCs decreased by 74 % between the two periods, while the part of 2nd generation COCs increased by 43 %. These findings are concordant with the French sale records of 2013 and 2014, which report a drop of 48 % for 3rd and 4thgeneration COCs and an increase of 32 % for the 1st and 2ndgeneration COCs, compared to 2012. These results reflect the positive impact of the 2013 alert.
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P 026

Medication Persistence of Dabigatran and Rivaroxaban Among Patients with Nonvalvular Atrial Fibrillation Initiating Anticoagulant Therapy in Early 2013 in France

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Introduction: The Non-VKA Oral Anticoagulants (NOAC), dabigatran and rivaroxaban, have been marketed for the prevention of stroke in

patients at risk with non valvular atrial fibrillation (nv-AF) as a more convenient alternative to Vitamin K antagonists (VKA), for which lack of persistence is a common problem. Although long-term persistence with anticoagulant is critical in ensuring efficiency of these drugs, so far only few studies have evaluated persistence of NOAC treatment using real-world data.

Aim: To describe non-persistence rates of dabigatran and rivaroxaban in the first year after treatment initiation using data from a large nationwide medico-administrative database, in nv-AF patients.

Methods: This study included VKA-naïve patients with nv-AF who initiated dabigatran or rivaroxaban between January 1st and June 30th 2013, using data from the French medico-administrative databases (SNIIRAM-PMSI). Patients presenting a contraindication or lost to follow-up were excluded. Patients were followed for up to one year until non-persistence to treatment defined as treatment discontinuation for at least 60 days after the end of days' supply of the NOAC, switch to another oral anticoagulant or death, whichever came first. Non-persistence rates at one year and time to discontinuation are given.

Results: Among the 12 093 dabigatran and 12 102 rivaroxaban patients included, 52,5 % and 53,9 % were men with a mean age of 73,6 ± 11,0 and 73,7 ± 11,1 years (15,2 % and 15,7 % ≥85 years old), respectively. During the follow-up, 23.4 % and 23.0 % of patients discontinued treatment for at least 60 days in dabigatran-and rivaroxaban-treated patients (median time to discontinuation: 148 and 138 days); 8.7 % and 5.2 % switched to another NOAC; 12.3 % and 9.8 % switch to VKA; 3.0 % and 3.1 % died, respectively. Among the group of patients who discontinued their treatment for at least 60 days, 19.7 % (N = 557) of dabigatran-and 17.0 % (N = 474) of rivaroxaban-treated patients resumed oral anticoagulant treatment (VKA or NOAC) within 4 months.

Conclusion: Although NOAC have advantages relative to VKA in terms of no laboratory monitoring and reduced interactions, in this "real-life" study on medico-administrative data, one-year persistence on NOAC therapy, dabigatran or rivaroxaban, appeared to be suboptimal in nv-AF patients initiating anticoagulant treatment in France in the first half of 2013.

P 027

Drug–Drug Interactions of Statins in Hospitalized Patients: Results from a Prospective Observational Study

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Introduction: The utilization of statins for their cholesterol-lowering and pleiotropic effects has increased considerably in the recent years. Following their increased utilization, controversies arose on their prescription patterns due to safety concerns. Statins' association with other drugs may enhance the risk of adverse reactions, of which the most frequent are the muscle-related ones due to elevated serum concentration of the statins.

Aim: To determine the prevalence of statins' potential drug–drug interactions (pDDIs) in hospitalized patients that had been prescribed statins before/during hospitalization and to find out how often they are associated with clinical outcomes.

Patients and methods: This prospective, non-interventional study performed in two internal medicine departments included patients with statin therapy before/during hospitalization. Data on each patient demographic characteristics, co-morbidities and treatment was collected from medical charts and interviews. We evaluated patients' therapy for pDDIs using Thomson Micromedex Drug Interactions checker and we ranked the identified DDIs accordingly. Each patient with statin treatment before admission was additionally interviewed in order to identify the clinical outcomes.

Results: In 109 patients on statin treatment we found 35 pDDIs of statins in 30 (27.5 %) patients, most of which in the therapy before admission (27 pDDIs). The pDDIs were moderate (20 pDDIs) and major (15 pDDIs). The drugs most frequently involved in the pDDIs were amiodarone (10 pDDIs) and fenofibrate (6 pDDIs). We identified 12 pDDIs of statins with CYP3A4 inhibitors and 4 pDDIs of statins with colchicine, a CYP3A4 substrate. Two of the patients with pDDIs reported muscle pain, both having additional risk factors for statin induced muscle toxicity. No other pDDIs had clinical outcome.

Conclusion: The prevalence of statins' pDDIs was high in our study, mostly in the therapy before admission, with only a small number resulting in clinical outcome (2 cases of muscle pain). Further prospective research on a larger number of patients would allow a more accurate estimation of the pDDIs' prevalence and a causal association with muscular effects.

P 028

Severe Cardiac Events Following Treatment with Trastuzumab in Women with Breast Cancer: A Meta-Analysis of Clinical Trials and Cohort Studies

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Introduction: Trastuzumab is associated with prolonged survival in women with HER2-positive breast cancer, but it may increase the risk of heart disease. However, the occurrence of severe cardiotoxicity in real-life settings has not been determined.

Aim: To estimate the frequency of severe cardiac adverse events (i.e., myocardial infarct, grade III–IV heart failure, left ventricular ejection fraction ≤40 %, or cardiac events leading to hospitalization) up to three years after trastuzumab initiation.

Methods: We searched MEDLINE, EMBASE and the Cochrane Library (1996 to January 2014). Eligible studies were clinical trials and cohort studies that reported the frequency of cardiotoxicity regardless of drug dose, treatment regimen, or follow-up length, with the exception of the

combination of target therapies. A meta-analysis was performed to calculate the weighted summary proportion of cardiac events and the respective 95 % confidence intervals (CIs) using a random-effects model.
Results: We screened 3826 abstracts for eligibility and included 58 studies (29,598 patients). Severe cardiac adverse events occurred in 3.00 % (95 % CI, 2.41–3.64), 2.62 % (95 % CI, 1.97–3.35) and 3.14 % (95 % CI, 2.12–4.37) of overall, early (EBC) and metastatic (MBC) breast cancer patients, respectively. In EBC, the proportion increased from 2.40 % in the first-year to a plateau of 3.17 % in the second year and 2.95 %, in the third year. In MBC, the proportion increased from 3.00 % to 3.68 % when trastuzumab was used as first-line or further-lines of therapy, respectively. In EBC, cardiotoxicity occurred in 2.90 % of patients treated with taxanes and anthracyclines, as compared to 0.92 % in patients treated with taxanes without anthracyclines. The occurrence of cardiotoxicity varied according to age, increasing from 2.31 % in individuals <50 years, to 3.46 % in those aged 50–59 years, to 4.91 % in those with >60 years of age. Cardiotoxicity was higher in smokers (5.3 %), patients with dyslipidemia (3.9 %), body mass index ≥25 (6.5 %), diabetes (6.2 %), hypertension (5.5 %), or positive history of cardiac disease (19.1 %). Clinical trials consistently reported lower cardiac toxicity rates than observational studies for women with either EBC (1.7 % vs 3.2 %) or MBC (2.8 % vs 4.4 %).
Conclusions: Following the initiation of therapy with trastuzumab, approximately 3 out of 100 patients develop severe cardiotoxicity after two years. Despite the benefits of trastuzumab in terms of life prolongation are well established, these should be weighed against the risk of severe cardiotoxicity, which may result in a serious detriment to the quality of life, particularly in elderly patients and those with cardiovascular risk factors.

P 029

Medication Errors Related to the Administration of Medicinal Gases in France: One of the Twelve French Never Events

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Introduction: The French National Agency for Medicines and Health Products Safety (ANSM) has set up in 2005 a department to collect and manage medication errors or potential errors related to medicinal products, and monitor those likely to present a Public Health risk. The "Medication errors' Guichet" enables healthcare professionals and patients to directly report to ANSM medication errors (ME) without adverse effect (AE) or near misses, in addition of reports with AE collected through the Pharmacovigilance System.
Aim: To quantify and analyse medication errors in relation with the administration of a medical gas and establish recommendations/ measures to reduce this risk. This type of medication error is part of the 12 French never events in hospitals.
Methods: We performed an analysis of medication errors (risk, near misses and patent) reported to the ANSM that have resulted to an AE or not, with requests in the Medication Error Database (from 01/01/2005 to 14/11/2014) and in the National Pharmacovigilance Database (from 01/01/1985 to 14/11/2014).
The analysis only focused on medicinal gases, which are drugs: the eight following active substances marketed in France (oxygen, nitrous monoxide, nitrous oxide, equimolar mixture of oxygen and nitrous oxide (EMONO), xenon and three halogenated gases: sevoflurane, isoflurane and desflurane).
Results: Since 1985, 42 reports have been identified, including 34 patent errors, leading to AE occurrence in 53 % of the cases (7 were considered as serious according to pharmacovigilance criteria, including 3 fatal cases).
The review of cases reported reveals that the majority of cases is caused by a confusion between two medicinal products: oxygen and EMONO cylinder (due to similar packaging). Other cases were mostly in relation with practice errors and non-compliance with precautions for use.
In France, more than 109 million of cylinders have been sold in 2013. Database queries revealed a significant under-reporting of medication error, probably due to the fact that healthcare professionals don't think that gases are drugs.
Conclusion: Risk minimization actions are currently studied to minimize risk of errors in order to limit their serious consequences: for instance, a sticker is currently developed to improve clarity on the labelling of EMONO cylinders in order to limit confusion with oxygen, a healthcare professionals communication.
To increase awareness among healthcare professionals and patients, training on the risks associated with the use of gas and information on these avoidable risks are essential.

P 030

Active Search for Adverse Reactions Using Medication Tracers

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Introduction: Spontaneous event reporting is the conventional method for the detection of adverse drug reactions (ADRs) and it depends on the knowledge and attitude of the healthcare workers. Because some medications, due to their indications, are used as antidotes for clinical conditions caused by medications, the active search for ADRs by means of the review of notes in the clinical records of patients who have received those medications helps identify ADRs that have not been reported spontaneously.
Objective: To identify, analyse and classify Adverse Drug Reactions using tracer medications given at the Fundación Santa Fe de Bogotá University Hospital during the period between October 2013 and March 2015.
Methods: Retrospective, descriptive, observational study conducted between October 2013 and March 2015 (18 months) with 700 patients who were given the tracer medications clemastine, naloxone or flumazenil. An active search was conducted in individual patient charts in order to understand the indication that prompted prescription and administration of the medication. The information was analysed in terms of the common international denomination (CID) of the suspect medication, the type of reaction according to the classification of the Uppsala Monitoring Center and the care setting where the reaction occurred (emergency room, hospital floor, ICU). Finally, ADRs were classified in accordance with the World Health Organization algorithm as definitive, possible, unclassified or unclassifiable.

Results: During the 18 months of the study, 700 patients were given clemastine, naloxone or flumazenil. In 7.6 % of cases, the medication was given against the symptoms of an ADR that was not reported spontaneously by the healthcare team (n = 53 ADRs).
Of the Adverse Drug Reactions, 77 % (41 cases) were type B, involving 28 medications. The largest numbers of cases were due to vancomycin and hydromorphone (6 cases, 11 % each). In the hospital setting, the largest number of non-reported ADRs (20 cases) occurred in the Emergency Department. In terms of causality, the analysis revealed 39.63 % probable causes and 60.37 % possible causes.
Conclusions: The active search resulted in the identification of ADRs that were not reported through the conventional system. It was an efficient way to detect adverse reactions, confirming the value of the active search as a method to supplement the spontaneous reporting system.
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P 031

Implementing Best Practices for the Safe use of Medications: It is Possible to Reduce Adverse Events, a 7-Year Experience

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Introduction: A priority at the Fundación Santa Fe de Bogotá University Hospital (accredited by Joint Commission International since 2010), has been the implementation of best practices for Patient Safety. Gaps are identified on a constant basis in order to ensure continuous improvement in accordance with international standards. Strategies for the safe use of medications are established by the Pharmacovigilance and Patient Safety interdisciplinary Committees.
Aim: To describe the experience with the implementation between 2008 and 2015 of best practices aimed at mitigating the risks associated with the use of medications and their impact on the occurrence of serious or non-serious adverse events.
Methods: The Pharmacovigilance Committee developed a self-evaluation tool based on JCI international standards and the ISMP Medication Safety Self Assessment® for Hospitals, and opportunities for improvement were established together with short and medium-term goals, accountability and improvement indicators.
Results: The following strategies were established as a result of the self-assessment:
Process implementation: Creation of awareness regarding medication errors, causes and safety barriers for mitigation during staff orientation; department participation in the situational analysis, and the identification of the causes of the events and improvement opportunities; evaluation of drug safety profiles before their inclusion as therapeutic options; implementation of a high alert medication system (labelling, centralized storage, information system alerts, etc.).
Staff training and patient empowerment: Training on the safe use of medications, drug interactions, role of the clinical pharmacist in event prevention, drug reconciliation, adequate use of antibiotics, patient and family participation in prevention, thromboprophylaxis, drug allergies, management of databases for the safe use of medications (Micromedex®).
Modifications to the information system: Implementation of a communication mechanism for potential drug interactions or risks for the patient between clinical pharmacists and physicians; visual alert regarding drug allergies and the need for dose adjustments when logging into the electronic clinical record; implementation of a patient education database (Care Notes®).
As a result of this implementation, serious medication errors dropped from 22 cases in 2009 to 10 in 2010, 17 in 2011, 7 in 2012, and 2 in 2013 and 2014. There was a 91 % reduction of serious adverse events in 5 years, and adverse events dropped from 297 in 2009 to 40 in 2014 (87 %).
Conclusions: The strategies put in place contributed to a significant reduction in drug-related adverse events at the Fundación Santa Fe de Bogotá University Hospital.

P 032

Medication Reconciliation Through Pharmacy Consultation: Criteria for Surgical Patient Prioritization

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Introduction: Flaws in medication reconciliation result in Patient Safety adverse events. Although the reconciliation process is required for all patients, there are patients with a higher risk of events associated with inadequate medication use. Sometimes, one-to-one consultation or advice from the pharmacy specialist is required, but pharmacy human resources are usually limited. Criteria for prioritizing patients at a higher risk must be identified.
Aim: To identify variables that need to be considered in order to prioritize surgical patients for whom pharmacy advice is required during the process of medication reconciliation at the Fundación Santa Fe de Bogotá University Hospital.
Methodology: A review was conducted in the literature pertaining to best practices and variables that influence correct reconciliation. A form for recording data from the patients was designed in order to make a characterization based on age, procedure and surgical specialty. The latter two variables were grouped under a single one called "Degree of surgical complexity". Chronic medications were characterized according to number of medications used, type of medication, dose, frequency and route of administration.
Results: Overall, 196 patients coming to the pre-anaesthesia consultation were included. Of them, 39 % were in the age group between 18 and 59, and 38 % were in the group 60 years and older, and they were the most representative. It was found that patients had difficulty filling the relevant fields such as procedure and surgical specialty. For this reason, surgical complexity could not be defined in 37 % of cases; 33 % of the patients had level II surgery, 15 % had level I surgery, and 14 % had level III surgery. The number of medications used ranged between 1 and 10, with a mode of 2; 25 % of the patients were using multiple medications (more than 4). The most prevalent medication and ATC pharmacological group were levothyroxine (36 %) and cardiovascular system (81 %), respectively. The criteria for prioritization were multiple medications, level III and IV

surgery, and age over 60. Based on those prioritization criteria, pharmacy is required to counsel 10 % of the population at a higher risk of adverse events associated with medication reconciliation.

Conclusion: Clinical pharmacy human resources may be optimized by establishing priorities for surgical patients at a higher risk of having adverse events associated with medication reconciliation.

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P 033

Empirical Evaluation of Statistical Signal Detection Based on Unexpected Time-to-Onset for Non-Vaccine Drugs in VigiBase

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Introduction: Statistical signal detection based on unexpected time-to-onset (TTO) has yielded promising results for vaccines [1, 2]. However, its potential usefulness for non-vaccine drugs has not been tested.

Aim: To evaluate the performance of TTO-based signal detection in identifying emerging safety signals with non-vaccine drugs.

Methods: A test set consisting of 179 historical EMA labelling changes (positive controls) and 2591 randomly selected drug-adverse drug reaction pairs not included in 2012 SPCs (negative controls) was used [3, 4]. Only TTO values between 0 and 60 days were considered, and all controls had at least two viable TTO values reported. Data were taken from VigiBase®, the WHO global individual case safety reports database, as of 31st December 2004, when the positive controls were still emerging safety signals [4]. The TTO distribution for a given reaction in relation to a given drug was compared to the TTO distribution for that reaction with all other drugs, using the two-sample Kolmogorov-Smirnov test [1]. Both the test's p value and its crude measure of distribution difference (D value) were evaluated. Predictive performance was measured as area under the receiver operating characteristics curve (AUC), and compared to that of the disproportionality metric IC025, and screening based on raw numbers of reports. TTO-based signal detection was also tested for inclusion into vigiRank, a data-driven multi-variable predictive model for emerging safety signals [4].

Results: The p and D value of the Kolmogorov-Smirnov test attained AUC of 0.519 and 0.617, respectively. The AUC of IC025 and raw numbers of reports were considerably higher, 0.747 and 0.702, respectively. The D value was tested for inclusion into vigiRank but not selected.

Conclusions: This study lends no support for the usefulness of statistical signal detection based on unexpected TTO for non-vaccine drugs.

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P 034

vigiRank Improves Real-World Signal Detection Performance: Prospective Results from International Pharmacovigilance

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Introduction: vigiRank is a statistical signal detection method for pharmacovigilance. It accounts not only for the observed versus expected number of reports on a drug-adverse drug reaction (ADR) pair, but also for the completeness, recency, free-text content, and geographical spread of its reporting. It offers conceptual advantages over sole reliance on disproportionality analysis, the current state-of-the-art approach, and evaluation against historical safety signals suggests improved empirical performance [1]. However, its impact on real-world pharmacovigilance is not known.

Aim: To evaluate vigiRank in prospective real-world signal detection by comparing its performance to that observed historically for disproportionality analysis.

Methods: In the spring of 2014, vigiRank was applied to data from VigiBase®, the WHO global individual case safety reports database, to identify drug-ADR pairs for initial assessment. The scope was restricted to WHO–ART critical terms and pairs reported by at least two countries. In the initial assessment each pair was classified as either labelled, non-signal, or worthy of in-depth assessment. Subsequently, in-depth assessment classified pairs as signals or non-signals. Both initial and in-depth assessment also permitted decisions to keep pairs under review, awaiting further reporting. A year after the initial data screen, the outcome of all assessments was analysed, and a comparison was made to corresponding historical metrics from 2009–2013, when first-pass screening of VigiBase relied on disproportionality analysis.

Results: 311 drug-ADR pairs identified by vigiRank were assessed initially, resulting in 10 signals (3.2 %) following the in-depth assessments. The historical performance for disproportionality-based signal detection was significantly worse with 37 signals out of 3518 initial assessments (1.1 %; $p < 0.01$). The 10 vigiRank signals came out of 27 in-depth assessments, corresponding to 8.7 % of the initial assessments; additionally, 153 were labelled, 116 were classified as non-signals, and 15 were kept under review. For disproportionality-based signal detection, the historical rate of initial assessments leading to subsequent in-depth assessment was about the same, 300 of 3518 (8.5 %).

Conclusions: Combining multiple strength-of-evidence aspects as in vigiRank significantly outperforms disproportionality analysis alone in real-world pharmacovigilance signal detection. These prospective results corroborate previous findings from retrospective analysis, jointly suggesting clear performance improvement relative to today's standard methods.

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P 035

Using Subgroup Analysis of Individual Case Reports to Identify Age-Specific Safety Signals—the Case of Thrombocytopenia and Lamivudine/Zidovudine

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Introduction: Many organisations use disproportionality analysis to identify suspected safety signals in collections of individual case reports. In this process, subgroup analysis has been shown to increase precision and sensitivity compared to crude and adjusted analysis, particularly in large databases1, but the mechanism for this improvement is not well understood.

Aim: To investigate examples of labeled adverse drug reactions (ADR) highlighted by subgroup analysis but not by crude or adjusted disproportionality analysis. To determine if subgroup analysis can identify labelled ADRs in specific age groups.

Methods: The analysis was performed in the WHO global ICSR database, VigiBase® as of January 2012 for 220 centrally authorized products. Statistics of disproportionate reporting (SDR) were identified using the lower 95 % credibility interval of the information component (IC), IC025. This was done in different ways: for the full data, adjusted by age, and for eight subgroups based on age (0–23 months, 2–11, 12–17, 18–35, 36–64, 65–74, 75+ years, and unknown age). Using ADRs listed in the summary of product characteristics (SPC) or core data sheets as positive controls, we identified SDRs that were highlighted only by the subgroup analysis and randomly selected five of these for further investigation.

Results: All reviewed combinations were relevant for the highlighted age group (s). One, thrombocytopenia under lamivudine/zidovudine treatment, concerned a mechanism specifically listed for the highlighted group2. Thrombocytopenia under lamivudine/zidovudine treatment had a positive IC025 for the age group 0–23 months. Review of the seven case reports showed that all children were exposed by transplacental route. Thrombocytopenia is probably induced by mitochondrial dysfunction 3, 4: The SPC lists this mechanism for anaemia and leucopenia in newborns exposed to lamivudine/zidovudine during pregnancy2.

Conclusion: Out of five investigated combinations one included a mechanism specific to the highlighted age group, showing that subgroup analysis can identify age-specific ADRs not otherwise highlighted. However, the scope of this study was limited and further research of this area is needed.

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P 036

Human Papilloma Virus Vaccines and Gastrointestinal Motility Disorders

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Introduction: Gastrointestinal motility disorders (GID) have been identified as a signal for human papilloma virus (HPV) vaccines using VigiBase®. HPV vaccines are indicated for prevention of premalignant genital and anal lesions caused by certain subtypes of HPV. Autonomic neuropathies can cause GID by involvement of the enteric nervous system [1]. Furthermore, HPV vaccines have been reported in association with autonomic nervous system dysfunction (AD) [2–3].

Aim: To investigate a relationship between GID and HPV vaccines.

Methods: Clinical review of ICSRs reporting the WHO–ART PTs "gastric dilatation" and "bowel motility disorder" included VigiBase up to 1 April 2015.

Results: 21 reports were identified. 14 cases reported "gastric dilatation"; 6 reported "bowel motility disorder"; 1 reported both terms. Reports were from US, UK, Germany, Sweden and Denmark. All cases were female. Ages 11 to 26 years; two reports had no information on age. HPV vaccine was suspect in all cases; two cases reported concomitant vaccines. Time to onset (TTO) was reported for 18 cases and ranged from 1 day to 2 years. Eleven cases reported TTO in relation to dose; the median onset after dose 1 in seven cases was 60 days and after dose 2 in seven cases was 19 days. Seventeen ICSRs reported additional information, as co-reported terms or in the narrative, potentially suggestive of AD (e.g presyncope). Nine cases reported diagnoses of AD (e.g Guillain-Barré Syndrome). Two cases reported diagnoses of gastrointestinal pathology (e.g ulcerative colitis). Outcome information was provided for seven cases; six were "not recovered". Two cases reported the placement of feeding tubes and one case reported the placement of a gastric pacemaker. Two cases noted a positive rechallenge; one with the term "vaccine positive rechallenge" and one with recurrent abdominal pain following subsequent doses of the vaccine.

Conclusion: This signal suggests a relationship between HPV vaccines and GID. Data on a biological mechanism and the incidence of AD in the target population is lacking. However, given the potential role of AD in a number of signals for HPV vaccine, further investigation is warranted.

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P 037

Characteristics of Adverse Event Reports After HPV Vaccination: a Global Perspective

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Introduction: Human papilloma virus (HPV) vaccines are indicated for use from 9 years for the prevention of premalignant genital and anal lesions caused by certain types of HPV. HPV vaccines have been incorporated into routine vaccination programmes worldwide, and evaluation of adverse events (AE) describing symptoms has been complicated by their relatively high frequency of incidence in the female, adolescent population. A characterisation of HPV reports in VigiBase® was therefore undertaken.
Aim: To identify patterns characteristic for individual case reports in females aged 9–25 years reporting adverse events after HPV vaccination.
Methods: Using all reports submitted to VigiBase, as of 1st January 2015, after excluding duplicates, the subset of reports concerning HPV vaccine in females aged 9–25 years was identified. These reports were contrasted to all other reports concerning females aged 9–25 years on multiple variables, such as report type, geographic source, MedDRA SOC and PTs, and outcome using the analytical framework vigiPoint. vigiPoint relies on shrunk odds ratios to identify key features of datasets [1].
Results: 45,876 HPV vaccine reports were compared to 510,996 reports on other medicines. Among the patterns highlighted for the HPV reports were more reports than expected from Malaysia, Italy, USA and less reports from Canada, Thailand, China. Highlighted SOCs in HPV reports were General disorders and administration site conditions, Nervous system disorders and Musculoskeletal disorders; highlighted SOCs in other reports were Hepatobiliary disorders, Reproductive system and breast disorders, and Psychiatric disorders. PTs most over-represented in HPV reports were injection site pain (13.5 vs 1.6 %), syncope (10.2 vs 1.3 %), injection site swelling (5.9 vs 0.7 %). PTs most under-represented in HPV reports were maculopapular rash (0.2 vs 2.0 %), metrorrhagia (0.1 vs 1.6 %), and face oedema (0.2 vs 1.3 %). There was no significant difference between groups in the proportion of reports reporting PTs of autoimmune or neurological diagnoses (e.g. multiple sclerosis). Also over-represented in HPV reports were many PTs describing nonspecific symptoms (e.g. headache, asthenia) and neurological dysfunction (e.g. gait disturbance, gaze palsy). HPV reports were less likely to report a fatal outcome.
Conclusion: HPV reports constitute almost 9 % of all AE in females aged 9–25 years. Reports after HPV vaccination more frequently contained symptoms of a nonspecific nature and neurological dysfunction than reports of other medications used in this population.
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P 038

An Innovative Software Tool for the Development, Implementation and Effectiveness Evaluation of Additional Risk Minimisation Measures

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Introduction: Additional risk minimisation measures (aRMMs) may be required to ensure patient safety in the product EU-RMP1, 2 or US-REMS2, 3. The implementation and effectiveness evaluation of aRMMs is important to ensure a positive benefit–risk balance for drugs with riskier profiles. We have developed software to simplify the development, implementation and evaluation of web-based aRMMs. The approach links the evaluation of individual tools and overall RMP/REMS into a single continuum.4
Aim: To assess whether the implementation and evaluation of aRMMs resulted in the effective understanding and reinforcement of key safety messages.
Methods: Software was used to develop, implement and evaluate the effectiveness of aRMMs as part of a non-interventional pan-European study. Two of the aRMMs deployed were a Healthcare Professional (HCP) Guide and Patient Information Brochure. Participating HCPs, caregivers and patients completed a short web-based survey to assess their understanding of the aRMMs.
Results: The use of a software-based platform with web-based aRMMs aligned with the increased preference for electronic tools over paper tools amongst HCPs and patients. It also allowed for more efficient development, delivery and effectiveness evaluation (compared to traditional paper-based tools), particularly when considering the multiple language requirements of the study. Using web-based aRMMs enabled more certainty in determining the use and distribution of aRMMs, tighter version control and reduced the costs of printing, reprinting and redistribution. It was also easier to collect real-time effectiveness metrics.
Conclusions: The use of a software platform with built-in aRMM development, deployment and effectiveness evaluation capabilities has been shown to offer several advantages over traditional paper-based methods. For example, the development of aRMMs in multiple languages was more cost effective, and enabled tighter version control. Additionally, web-based aRMMs can support wider availability (the number of available paper copies can be limited), and allow interactive feedback and data capture mechanisms. Web-based aRMMs also fit with the increasing demand from HCPs and patients for applying the internet to health-related applications.
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P 039

Switch Between TNF-Antagonists: a Population Based Study

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Introduction: Two biosimilars of infliximab have been commercialized in Europe since February 2015. These drugs have been shown to be similar to the reference one and are therefore recommended for the same indications. Nevertheless, as for other biosimilars, a concern is often raised on the acceptability of switching in patients already treated with the reference product. This worry does not take into account that switching between different reference products of the same therapeutic category might be relatively common in clinical practice despite the absence of comparative studies.
Aim: This study aimed at quantifying the proportion of patients chronically treated with TNF-antagonists drugs who switched between different substances.
Methods: The study was conducted in the Umbria region (about 900,000 inhabitants), Italy, in the period between 1 January 2011 and 31 December 2013. All subjects who received at least one prescription of TNF-antagonists (ATC: L04AB) during the study period were included in the analysis. The database of drug prescriptions covered by the NHS and the regional archive of residents in the Umbria region were used. The probability distribution of switching was related to the months of treatment in a survival analysis that included only patients with at least two prescriptions of TNF-antagonists. A sensitivity analysis was performed on the cohort of incident users (patients with the first prescription of TNF-antagonists without other prescriptions of the same drugs in the previous 6 months).
Results: During the study period 1227 subjects received at least one prescription of TNF-antagonists (prevalence: 1.4 per 1000 inhabitants). Users had a median age of 54 years and were more frequently female (58.0 %). The most commonly prescribed TNF-antagonists were etanercept (n = 544, 44.3 %), adalimumab (n = 536, 43.7 %) and infliximab (n = 110, 9.0 %). Among the 1179 patients with at least two prescriptions of TNF-antagonists, 15.0 % (n = 176) had at least one switch. The probability of switching increased with the duration of treatment: from 10 % of users within 12 months of treatment to almost 18 % within 24 months. The probability of switching was higher among incident users (n = 548) reaching 25 % within 24 months of treatment.
Conclusion: Switching between TNF-antagonists over time is common especially among incident users. Given that TNF-antagonists are generally not compared before marketing, there should be no objection in switching between products-reference drugs and biosimilars-that were assessed in a thorough comparability exercise.

P 040

Plantar Psoriasis Associated with Olmesartan

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Introduction: Psoriasis is a chronic inflammatory skin disorder which may be initiated or exacerbated by some drugs. The most common medications known to induce psoriasis include lithium, gold salts, beta blockers and antimalarials. We report an exceptional case of plantar psoriasis associated with olmesartan.
Case Report: A 57 year-old woman, with no personal or familial history of psoriasis, was diagnosed hypertension on 2010. She was prescribed a fixed combination of olmesartan (20 mg) and hydrochlorothiazide (25 mg), 1 pills/day. On October 2014, she developed erythematous scaly plaques with painful fissuring on her soles. The physical examination showed hyperkeratosis with fissures involving at least 50 % of every plantar surface. Nails and mucosae were normal. This was compatible with plantar psoriasis. There was no context of stress or infection. She was prescribed topic corticoid and maintains antihypertensive drugs. Her skin condition worsened. On January 2015, olmesartan and hydrochlorothiazide were replaced by fixed association of perindopril and amlodipine. A UVA therapy (3 times a week) was started on February 2015. Hyperkeratosis and pain decreased significantly.
Discussion: The responsibility of olmesartan in inducing psoriasis was evaluated as possible based on Naranjo scale with a score of 3. The responsibility of hydrochlorothiazide was valuated as 2. Naranjo scale score was lower for HCTZ because there was no report of psoriasis induced neither by this drug nor by thiazide diuretics. Sartans were reported as a possible causative agent in inducing or exacerbating psoriasis: 11 cases of sartan induced or exacerbated psoriasis were published. In these cases symptoms occurred in a delay of 1 week to 9 months after initiating the treatment. Our patient developed the event 4 years after starting.
Among the 11 patients reported in literature, the suspected drugs were losartan, candesartan, irbesartan and valsartan. Olmesartan was the drug prescribed in our patient. In literature lesions predominated in the sun-exposed areas and severe ungual involvement were present. Our patient psoriasis was localized in soles.
Conclusion: Our case reports an exceptional localization of psoriasis probably induced by olmesartan after 4 years of use.

P 041

Lyell Syndrome After Rituximab Infusion

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Introduction: The rituximab antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. It's used in the treatment of low-grade non-Hodgkin's lymphoma and diffuse large B-cell lymphoma. Side effects associated with rituximab were mainly mild infusion-related reactions such as fever, nausea and headache. The cutaneous side effects of rituximab are frequent but usually not serious. Severe skin eruptions have been rarely retrieved in literature.
We report a case of Lyell syndrome associated with rituximab and evaluated according to the French method of imputability of Begaud and al.
Case Report: A 55-years old man with an insulin-dependent diabetes since 15 years was diagnosed with follicular lymphoma in 2006. He had no atopic history.

He was taken rituximab since two years as a single treatment. The last infusion was taken on the thirteen December 2014. On the 3rd of January 2014, the patient had erythematous eruption with pruritus. Progressively, he presented flaccid blisters and diffuse erosions. He was hospitalized in unit care of burns. Nikolsky sign was positive and the overall body surface area detachment was above 50 %. The diagnostic of Lyell syndrome or toxic epidermal necrolysis (NET) have been carried. The patient had stationary skin state during one week and then progressively had skin healing (during 2 weeks)

Conclusion: The responsibility of rituximab was retained in front of compatible chronology:

- A delay of onset 20 days after the last infusion of rituximab (median half-life: 22 days)
- The good evolution in two weeks.

The pathophysiology of the Lyell syndrome has not been fully elucidated, it is commonly associated with the medication use. Since rituximab was the only drug used, he was stopped and the patient didn't develop any similar symptoms for 6 mO 72onths of follow-up.

In literature cases of NET or Stevens Johnson are exceptionally reported with rituximab.

P 042

Digital Ischemia Induced by Gemcitabine and Cisplatin

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Introduction: Gemcitabine is a potent cytotoxic agent used in the treatment of many solid tumours, sarcomas and lymphomas [1]. Vascular toxicity is a rare but serious side effect of this chemotherapy. This Vascular toxicity to gemcitabine seems to be underreported. We report a case of patient who developed severe digital ischemia during combination gemcitabine/cisplatin chemotherapy for non-small-cell lung carcinoma.

Case report: A 67-year-old man developed advanced non-small-cell lung carcinoma with bone metastases in October 2014. He was heavy smoker in the past. He had no symptoms of arterial disease over the previous 10 years. In January 2015, he was treated by gemcitabine (700 mg/m^2) and cisplatin (80 mg/m^2) every week. Seven days after the second cycle of chemotherapy, he presented severe pain, paresthesia, oedema, and punctate haemorrhagic lesions in four digits of his left hand. At the fingertips of his hand, haemorrhagic and partly ulcerative lesions were found. Chemotherapy was stopped and fractionated heparin subcutaneously was prescribed with oral therapy including vasodilators and antiplatelet drugs were started. Despite this symptomatic treatment, ischemic changes became evident and digital ischemia progressively worsened and gangrenous changes developed in multiple fingers. Digital amputation was necessary.

Conclusion: Digital ischemic events associated with gemcitabine chemotherapy are described in literature, especially when used in combination with platinum salts and in patients with tobacco-associated cancers. Therefore, in patients with known risk factors for peripheral arterial occlusive disease, like dyslipidemia, arterial hypertension, diabetes or tobacco smoking, thorough the examination of peripheral pulses should be performed before the initiation of gemcitabine or platinum-gemcitabine association. Discontinuation of gemcitabine and immediately therapy with prostacycline was necessary if painful trophic digital changes develop while on therapy with gemcitabine.

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P 043

Angioedema Associated with Angiotensin-Converting Enzyme Inhibitor: A Retrospective Study

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Introduction: Angiotensin converting enzyme inhibitors (ACEI) agents were proven to be effective in many cardiac diseases especially heart failure and lowering blood pressure. ACEI can cause many side effects such as hyperkalaemia, hypotension, renal failure, hepatitis, dysguesia, cough and angioedema (AE) [1]. Their most troublesome, side effects for patients are cough and angioedema. Angioedema is a rare complication but nevertheless a very dangerous one.

The aim of our study was to report all cases of angioedema associated with ACEI agents notified to the Tunisian National Centre of Pharmacovigilance.

Methods: It was a retrospective study involving all angioedema associated with ACEI agents, notified to Tunisian National Centre of Pharmacovigilance between January 2009 and December 2014. We considered the cases in which ACEI agents had the most important imputation score alone or in association with other drugs. The cases were analysed according to Begaud method of imputation [2].

Results: There were 25 patients including 13 women and 12men. The age varied from 27 years to 83 years. Seven patients had a history of allergy and five patients had a history of drug allergy. ACEI was prescribed alone in 4 cases and associated with other drugs in 21 cases. Captopril was the most implicated drug in the genesis of AE. The delay of AE ranged from20 minutes to several years after beginning of ACEI. In our patients, AE involves the face, lips, tongue, eye and genital organs. AE was associated with urticaria in 7 cases and dyspnoea in 4 cases. The outcome was favourable after stopping ACEI in 12 cases. Ten AE regressed in spite of continuing the ACEI. In3 cases, there were recurrences of AE when ACEI was not stopped. Seven patients received treatment with antihistamine during AE, but in 18 cases there was an improvement without antihistamine treatment.

Conclusion: Stopping ACEI is necessary in patients who experienced angioedema induced by ACE-I. Maintaining of the ACEI may expose the patient to more severe reactions. Switching to another ACE-I medication is contraindicated.

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P 044

Use of Triggers in the Characterization of Adverse Drug Events in a Pediatric ICU

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Introduction: Chart review using triggers has shown to be more efficient than other methods for the detection of adverse drug events (ADEs). However, there are few studies on their use on pediatric patients, especially in Pediatric Intensive Care Units (PICU).
Aim: (1) To test the applicability of the chart review using triggers in the PICU of a medium complexity university hospital in Sao Paulo, Brazil; (2) To characterize the adverse events occurring in the PICU.
Methods: Charts of patients admitted to the PICU were prospectively reviewed by two reviewers. An analysis based on the predictive value of triggers was performed to verify the applicability of the method. Data about the ADE and the patients involved were analysed to characterize the ADEs. A statistical analysis was performed to verify the association between sex, age and length of stay with the occurrence of at least one ADE.
Results: The charts of 77 patients were assessed throughout a period of 123 days. Thirty-two (32) ADEs were found, which occurred more frequently in females (65.6 %) aged less than 12 months (65.6 %) and with more than 11 days of hospitalization (55.4 %). The odds ratio for the occurrence of at least one ADE was 0.974 (95 % CI: 0.954–0.994) for age in months and 1.073 (95 % CI: 1.013–1.138) for days of hospitalization, whereas a significant relationship with sex was not found. The most frequent events were "oversedation", "hypotension", and "abstinence", mainly related to midazolam (sedative) and fentanyl (opioid analgesic). During the period, a total of 217 triggers were found in the charts, 20 (9.2 %) of which being associated with at least one ADE. The trigger with the best predictive value was "Oversedation/lethargy/fall/hypotension", associated with 31.3 % of the ADEs.
Conclusion: The method has shown to be a useful tool with a significant detection of ADEs in the PICU; however, changes are necessary to improve detection in this specific ward. The characterization of ADEs and the identification of potential risk factors for the occurrence of ADEs were possible but limited, due to the small sample size and small number of ADEs detected. It is necessary to carry out a study with a larger sample size and a longer period of review to improve the method.

P 045

Web-Based Intensive Monitoring of Metformin

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Introduction: Knowledge of time course, management and outcome of adverse drug reactions (ADRs) is important for a better understanding of the safety profile of a drug. The Netherlands Pharmacovigilance Centre Lareb has developed a web-based intensive monitoring system which tries to capture this data.
Aim: To study the safety profile of metformin in daily practice.
Methods: We performed a prospective, observational cohort study. First-time metformin users were recruited through pharmacies between 1 February 2008 and 1 April 2012. Patients were invited to complete six web-based questionnaires 2 weeks, 6 weeks, 3 months, 6 months, 9 months and 12 months after the start of metformin. Information was gathered about patient characteristics, ADRs and drug use. Drugs were coded using the Dutch drug dictionary (Z-index). Indications and ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.
Results: A total number of 2490 patients (59 % male, 41 % female) signed up for the study. Mean age of the study population was 59.2 years (SD 10.9, range 12–89 years). The response rates for the first up to the sixth questionnaire were 67, 66, 61, 54, 49 and 47 %, respectively. At baseline 1898 patients (76 %) were using one or more concomitant drugs. A total of 860 patients (35 %) reported the occurrence of at least one possible ADR related to the use of metformin. ADRs reported in $\geq$1 % of the patients were diarrhoea (14.9 %), nausea (6.4 %), abdominal discomfort (4.7 %), flatulence (3.7 %), headache (3.3 %), abdominal pain (2.3 %), dizziness (2.2 %), fatigue (2.0 %), constipation (1.5 %), pruritus (1.2 %), abdominal pain upper (1.1 %) and dysgeusia (1.0 %). The median latency time for these ADRs was 1–6 days, with exception of pruritus with a median latency time of 16 days. The percentages of patients who reported the presence of an ADR were 27, 30, 28, 24, 20 and 19 % for the six successive questionnaires. This indicates that a large proportion of the patients was suffering from ADRs in the period of 2–6 weeks after the start of metformin. The majority of the patients (76 %) undertook no action regarding metformin after the occurrence of an ADR. This suggests that the overall impact and severity of ADRs was relatively low, so that no action was required.
Conclusion: This study gives insights in the safety profile of metformin in clinical practice. Future research should focus on the impact of ADRs on patient's quality of life, to gather even more information about drug related ADRs.

P 046

A Harmonised Scheme to Support Developing Risk Management Guidelines Beyond ICH Countries

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Introduction: The principles of proactive pharmacovigilance stated in the ICH E2E Guidelines remain to be enforced in a large number of non-ICH countries. To address this issue, a Special Interest Group (SIG) of the International Society of Pharmacovigilance (ISoP) was created early 2015. Whilst the primary objective of this group is to elaborate innovative methods for risk minimisation applicable to non-ICH countries, setting a regulatory framework was identified as a necessary preliminary step. The purpose of the present work is to provide an open source Customisable RM Guideline Template that any non-ICH health authority (HA) may decide to use, on a voluntary basis to create a Risk Management Guideline.
Methods: To address diverse country needs, the Customisable RM Guideline Template proposes different options corresponding to variable amounts of documentation to be reviewed by HA depending upon available resources. However, the proposed options are harmonised with E2E principles and consistent with the concept of Country-Specific Annex created by Australia's TGA.
Results: The customisable template includes the following sections: 1. General principles. 2. Roles, responsibilities and obligations of (a) health authorities, (b) medical institutions, (c) health care professionals, (d) applicants or product license holders during the development phase, at submission, and after submission, (e) contract partners and (f) product users. The Template guides the preparation of a concise country-specific risk management document also customisable depending upon country expectations and resources available for document review. Risk minimisation activities are classified according to three categories: A: Additional educational risk minimisation activities; B: Structured/intensified collection of safety-related information; C: Restriction of prescription/delivery. The implementation and enforcement of country guidance resulting from the use of this customisable template is not described because those aspects are specific of each country pharmacovigilance system.
Discussion: The Customisable RM Guideline Template is aimed to guide countries setting a regulatory framework for risk management and risk minimisation, however, it does not provide example of methods applicable to a large array of non-ICH countries. Designing such methods is the objective of the ISoP Special Interest Group on Risk Minimisation Methods for Asian Countries. The methods elaborated by the group will be delivered stepwise during the subsequent ISoP events of the upcoming 18 months then published to serve a wider array of countries.

P 047

Patterns of Spontaneously Reported Adverse Drug Reaction in Bhutan

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Introduction: The pharmacovigilance system in Bhutan was established in 2005 after the development of Bhutan medicine rules and regulation. National pharmacovigilance centre (NPC) function under drug regulatory authority (DRA) and monitor adverse drug reaction (ADR) reports. Adverse drug reactions are reported spontaneously and voluntarily by the healthcare professionals.

Aim: The aim of the study is to determine the pattern of adverse drug reactions (ADRs) by spontaneous report.
Methods: It is a descriptive study on all the ADR reports that were collected between 2007 to May 2014 in NPC. The descriptive statistics was analysed by using SPSS version 20. The characteristics of ADR reports were described based on (1) demographical distribution of the patients, (2) sources of reports and the healthcare professional (3) suspected drug classification on Anatomical Therapeutic Chemical (ATC) classification code, (4) system-organ classes according to the Council for International Organizations of Medical Sciences (CIOMS) criteria.
Results: The total of 17 ADR report were available during the time of study. Out of which 11 (64.7 %) were female and 6 (35.3 %) were Male, 4 (23.5 %) are within the age range 1–20 years, 5(29.4 %) within 21–40 years, 4(23.5 %) within 41–60 years, 3 (17.6 %) within 61–80 years and 1 (5.9 %) did not mention. Overall 7 (41.2 %) of reports came from national referral hospital following 6 (35.3 %) reports from district hospital and 4 (23.5 %) from regional referral hospital. Highest number of report were reported by pharmacist including pharmacy technician 8 (47.1 %), 4 (23.5 %) reported by physician and 4 (23.5 %) by nurse. Most of the adverse events were from drugs used in anti-infective for systemic use 12 (70.6 %), followed by alimentary tract and metabolism 4 (23.5 %) and nervous system 1 (5.9 %). When reaction were classified according to CIOMS criteria, 13 (76.5 %) reaction were related to skin and appendages, 3 (17.6 %) respiratory system disorders and 1 (5.9 %) central and peripheral nervous. 11 (64.7 %) reaction were serious and 6 (35.3 %) were non-serious. 5 (29.4 %) of reaction caused life threatening, 3 (17.6) caused Prolonged hospitalization and 3 (17.6) were Medically significant.
Conclusions: Although this study was descriptive on 17 reports, it was known that most of the ADRs were caused due to anti-infective drug and most of the reaction were related to cutaneous in Bhutanese society. Therefore the healthcare professional need to be alert while administering anti-infective medication. As this is the only study conducted on pattern of ADRs in Bhutan further study on knowledge about ADRs and pharmacovigilance by healthcare professional is required.

P 048

Management of Medication Errors/Overdosage with Paracetamol (Acetaminophen) in France

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Introduction: The French National Agency for Medicines and Health Products Safety (ANSM) has set up in 2005 a department to collect and manage medication errors or potential errors related to medicinal products, and monitor those likely to present a Public Health risk. The "Medication errors' Guichet" enables healthcare professionals and patients to directly report to ANSM medication errors (ME) without adverse effect (AE) or near misses, in addition of reports with AE collected through the Pharmacovigilance System.
Aim: To quantify and analyse medication errors, non-voluntary overdosage in relation with oral use of paracetamol (oral dry form containing paracetamol alone or in combination medicines) and establish recommendations/ measures to reduce risks. Medication error with paracetamol is part of the 12 French never events in hospitals.

Methods: We performed an analysis of medication errors (risk, near misses and patent) reported to the ANSM with paracetamol (oral dry form) that have resulted to an AE or not, with a request in our Medication Error Database (from 01/01/2011 to 13/04/2015).
Results: Since 2011, 330 reports have been identified with paracetamol, including 20 risk of medication error, 20 near misses and 290 patent errors, leading to AE occurrence in 79 % of the cases (107 were considered as serious according to the pharmacovigilance criteria).
The medication errors review regarding use of paracetamol reveals that the majority of cases is administration error (90 %) and caused by patient due to human error (90 %) at home.
Most of medication error led to an overdosage (78 %) that could in some cases be associated with liver injury or death. Most of cases led to an overdose were reported in adults, in a context of severe pain (especially dental pain and headache 40 %), or by a lack of adaptation dosage (16 %) (based on weight, renal insufficiency or alcoholism).
In 2014, an annual average of 73.7 g of paracetamol (61.7 g from medicines containing only paracetamol and 12 g of a drug of paracetamol in combination with other substances) is consumed by a French patient.
Conclusion: Risk minimization actions are currently studied to minimize risk of occurrence of those errors and limit their consequences: for instance, a new labelling, identical for all oral dry form of paracetamol could be proposed, and a communication to patient and/or HCP.
To increase awareness among patients, information and education on the risks associated with the use of higher dose of paracetamol are essential.

P 049

Can Drug Disposal Flow Diagrams Contribute to the Control of Pharmaceuticals in the Environment?

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Introduction: A number of strategies have been implemented in different parts of the world to tackle the presence and persistence of pharmaceuticals in the environment. In order to effectively implement successful strategies in any setting, the context of the community in which the strategy is to be implemented is important. The context will provide information on what may or may not be successful and how to tackle any challenges to ensure cost effectiveness and sustainability. This abstract examines the feasibility of drug disposal flow diagrams to control pharmaceutical waste in the environment in Ghana.
Aim: The aim of this work is to assess the relevance and feasibility of Drug Disposal Flow Diagrams (DDFD) as a tool to control pharmaceutical waste in Ghana.
Method: A pilot study was conducted in 30 pharmacies in 2 urban areas—Accra and Kumasi—in Ghana to assess the disposal practices of community pharmacies and consumers with respect to their unused and expired medicines. Key informants were also interviewed on the disposal practices of pharmaceutical manufacturers, wholesalers and distributors. The information so gathered was put together in a flow diagram. This diagram gives a pictorial illustration of how safely consumed and unconsumed (unused and/or expired) pharmaceuticals are collected, transported, treated and reused or otherwise disposed of.
Results: The results indicated that DDFDs are a feasible tool for controlling pharmaceutical waste in Ghana. The tool highlights areas that require focused intervention to achieve maximum impact. For example, since 57 % of waste is disposed of unsafely in the local areas where they are generated and 29 % is discharged untreated into receiving waters, focus on these areas will yield the best outcomes.
Conclusion: The DDFD incorporates the context and outcomes for the methods of disposal currently in place. It provides relevant information for policy formulation and the implementation of effective strategies. DDFDs are adaptable and can be used in multiple settings including in resource constrained countries like Ghana where its feasibility has been demonstrated as it identifies areas for focused interventions.

P 050

Co-Prescription of Renin-Angiotensin System Acting Agents and Assessment of Serum Creatinine and Potassium in Patients with Renal and Diabetic Disease

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Introduction: Due to concerns that combining different renin-angiotensin system (RAS)-actingagents could increase the risk of hyperkalaemia and renal failure compared with RAS-acting monotherapy, starting from September 2014 the dual inhibition of the RAS is not recommended anymore in EU, unless if considered absolutely essential, and carried out under specialist supervision with close monitoring of renal function, electrolytes and blood pressure [1–4].
Aim: To describe the extent of co-prescription of RAS-acting agents in patients with renal and diabetic disease and to examine to what extent laboratory monitoring of serum creatinine, urea, potassium, and sodium concentration is performed before prescribing these agents.
Methods: We performed a retrospective study in an electronic health database, including all patients hospitalized between January 2013–June 2014, with a prescription of a RAS-acting agent at hospital discharge: an angiotensin-converting enzyme inhibitor (ACEi), an angiotensin receptor blocker (ARB), or a combination of the two. Variables like demographics, co-morbidities, co-medications, proportion of patients with the above mentioned parameters measured, and with high values before discharge were analysed.
Results: Out of a total number of 10,315 patients hospitalized during the study period, 1281 (12.42 %) were prescribed RAS-acting agents at hospital discharge: 1003 (9.72 %) were prescribed an ACEi, 254 (2.46 %) an ARB, 24 (0.23 %) were co-prescribed an ACEi and an ARB. Among patients with diabetes and renal disease the co-prescription of ACEi with ARB was higher compared to the overall population (0.84 % and 0.82 %, respectively). All patients with diabetes and renal disease had their creatinine, urea, potassium and sodium concentration monitored before prescription. Creatinine values (as per the last measurement before discharge) higher than 1.7 mg/dL were found in 3.76, 8.57 and 21.43, and in 32.26, 53.85 and 60 % of patients discharged with an ACEi, ARB and a combination of the two, in the diabetic andrenal patients, respectively. No

study patients in the dual therapy group had potassium values higher than 5.5 mmol/L.

Conclusion: The co-prescription of RAS-acting agents was found to be higher in patients with diabetic and renal disease compared to overall population, and in patients with altered creatinine values compared to patients receiving monotherapy, increasing the risk of further renal deterioration.

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P 051

ISoP Israel Project to Address Public Health Issues Through a National Multi-Lateral Collaborative Risk Management Plan: Time to Move Forward

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Introduction: Major Public Health Issues remained unsolved or insufficiently addressed such as the risk of bleeding with anticoagulants. Especially where multiple stakeholders are involved in the treatment, the lack of coordination can jeopardize the patient's safety. ISoP Israel Chapter has designed a project to address such multidisciplinary safety issues in building a new model relying on Risk Management approach.

Aims: Design and implement a collaboration of all stakeholders to advance pharmacovigilance through a national risk management plan.
Demonstrate project feasibility and efficiency in preventing/minimising the risk.

Method: The proactive approach of Risk Management Plan (RMP) has been recognised as the most efficient way to prevent and minimize the risks but usually is required only from industry. ISoP Israel project is to federate all stakeholders in a national campaign and a national multidisciplinary RMP during a period of 2 years, under supervision of the Ministry of Health. Stakeholders are the Health Management Organisations (Koupot Holim), hospitals, Healthcare Professionals, industry, academy, research in pharmaco-epidemiology and scientific associations (i.e. Clinical Pharmacology, ISPOR, PDA, Pharma Israel, patients associations, etc.).
The milestones for 2015–2017 are:

1. Constitution of the Scientific Committee and Monitoring Board
2. Defining the project and the stakeholders roles, choosing the Public Health Issue
3. Presentation of the project to ISoP Annual meeting, 2015
4. Writing the National Risk Management Plan
5. Organising an ISoP Israel symposium in Israel under the umbrella of the MOH (Dec 2015-Q1-2016)
6. Set up of the national campaign 2015–2016
7. Preliminary results presentation: ISoP Annual meeting 2016 and ISoP Israel symposium Q1-2017
8. Final results presentation
    a. ISoP Annual meeting 2017 with ISoP Israel satellite symposium
    b. ISoP Israel conference Q1-2018
9. Board and MOH final debriefing 2018

Results: The project is at the feasibility stage.

Conclusion: First steps are taking place in Israel to advance the vision of a national pharmacovigilance and risk management plan to improve the patient's safety. The main challenges will be:

- Enhancing the communication between healthcare professionals
- Gathering different interests and points of view and uniting them around a common goal
- Creating an efficient/cost effective tool for handling safety issues
- Establishing the basis for a universal model

We believe that the Israeli medical and scientific community is ready and well equipped to lead this project to its target and to outline the way for more pioneering and innovative projects.

P 052

Description of a Process to Optimize Diagnosis and Management of HIT in a University Hospital

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Introduction: Use of heparin is common in hospitalized patients, whether prophylactic or curative. When platelet count decreased during the heparin therapy, a heparin-induced thrombocytopenia (HIT) may be suspected by physicians. In this case, heparin should be immediately stopped and substitutive anticoagulation treatment should start. However, in such patients, other differentiation diagnosis of thrombocytopenia are possible, such as underlying disseminated intravascular coagulation, infection, hematotoxic drugs, surgery, extracorporeal circulation… If HIT is diagnosed, heparins should be definitively contra-indicated. The choice of an alternative anticoagulant is difficult, regarding some constraints (cost, renal function, availability to laboratory monitoring…). Actually, the quality of collected information for HIT diagnosis is essential to conclude.

Objectives of the study: To describe the process of diagnosis and management for HIT suspicions in our hospital.

Material and Methods: For any HIT suspicion, a tripartite team has been organized since 10 years, involving the pharmacovigilance centre, the hemostasis laboratory and the pharmacy. The aim of this organization is 1/ to collect all information (both biological and clinical) mandatory for HIT

diagnosis 2/ to analyse and conclude about HIT suspicion and 3/ to propose, if necessary, substitutive anticoagulation therapy. The collected information followed the clinical probability scoring system, the 4Ts, such as grade of thrombocytopenia, timing of thrombocytopenia occurrence, thrombosis, and the possibility of other etiologies.
Results: From January 2009 to December 2014, 469 HIT suspicions were analysed. 39.2 % (184/469) were excluded by multidisciplinary team with collected information, before laboratory tests. Among 285 other cases (60.8 %) an anti PF4-heparin antibody searched for by ELISA has been realized: 195 results (68.4 % of lab tested patients) were negative, leading to exclude HIT diagnostic, and 90 cases (31.6 % of lab tested patients) were positive, leading to stop heparin therapy. Among 469 cases, HIT diagnostic was confirmed in only 48 cases (10.2 %) by platelet serotonin-release assay and platelet count raised up after heparin stop.
Conclusion: Clinical probability was low in 39.2 % patients studied, allowing HIT direct exclusion only with collected information and heparin continuation. In the other subjects, laboratory tests were performed leading to HIT positive diagnosis in only 10.2 % of studied subjects. This study demonstrates importance of collected clinical information's quality to establish a diagnostic leading to contraindicate a common therapeutic class such as heparin therapy.

P 053

Dietary Supplements Used In Bodybuilding: Possible Serious Adverse Effects

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Background: Consumption of dietary supplements has been increasing for more than ten years. Athletes lack information on dietary supplements, although 45 % to 52 % take them to improve their health.
Objective: To draw attention to the serious risks that may be associated with use of dietary supplements. We present three cases reported in our region by clinicians who observed adverse effects in bodybuilders after supplement consumption.
Methods: Three cases were spontaneously reported to the pharmacovigilance centre of the Nord-Pas-de-Calais region in Lille, France. We collected data on the dietary supplement used, its composition, duration of use, type of adverse effect, and alternative diagnoses. We then carried out a literature search in PubMed, MEDLINE and other search engines using the keywords sports, resistance training, dietary supplements, stroke, hepatotoxicity.
Results: Three young patients aged 31, 32 and 45 years, with no particular history, took dietary supplements as part of their bodybuilding programme. The first patient presented with bilateral sylvian micro-infarcts after taking synephrine for one month (Animal Cuts). The second presented with a right thalamic infarct after taking a nitric oxide precursor for one year (NO-XPLODE). The third presented with acute cholestatic hepatitis after taking whey proteins for 6 to 12 months (Aptonia). In all cases, the differential diagnoses were less probable. The symptoms rapidly regressed when the product was discontinued, with no recurrence at 2, 4 years and 4 months.
Conclusions: All athletes should be asked about consumption of dietary supplements and informed of their potential toxicity.

P 054

Adverse Events of Antibiotics and their Management in a Department of Infectious Disease

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Introduction: Antibiotics adverse events (Atb-AE) represent an important part of drug related iatrogenic problems, whose consequences are poorly evaluated. Because of the heterogeneity of the different antibiotic families, this drug-class can cause many AE with various presentations.
Aim: The aim of the study is on one hand to make an inventory of AE resulting from the use of antibiotics and on the other hand to evaluate risk factors for occurrence of AE.
Methods: We conducted an observational prospective study during seven months in a department of infectious diseases (20 beds). In all cases of pharmacovigilance, the regional pharmacovigilance centre (RPC) was contacted and gave advices. Management and outcome of the AE were monitored.
Results: Three hundred and forty eight patients were hospitalized in the department during the study, 63 of them presented at least one Atb-AE. Overall we collected 84 Atb-AE: 21 consisted in hematological disorders, 17 in cutaneous, 13 in renal, 13 in hepatic, 12 in gastrointestinal, 6 in neurological and 2 had an interaction with the immune system. Previous renal or hepatic failures appear to be risk factors for developing an Atb-AE, as well as the increase of the average length of stay in hospital. Use of beta-lactams leads to few AE, whereas fluoroquinolones, rifampicin and antituberculosis treatment highly provide AE. Management of AE depends on the disorder and its severity. In case of a minor Atb-AE, monitoring this abnormality allows the maintenance of the antibiotic with regularly checking. This is the case for hematologic, hepatic and renal disorders. For hepatic disorders, a reduction of the dose of antibiotic is usually enough to normalize the disorder. On the contrary in our study the treatment is stopped in the majority of cutaneous disorders. Neurological and gastrointestinal disorders do not usually require to stop the treatment.
Conclusion: Risk factors of developing an AE to antibiotics were identified. Protocols of management of AE are hard to establish because of the heterogeneity of patients, infectious diseases, germs, length of treatment and alternative choices of treatment, hence the importance of expertise of RPC in helping prescribers to maintain or not a treatment when an AE appears.

P 055

Detection of Off-Label Drug Use: a Role for Pharmacists?

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Introduction: Off-label prescribing is extremely widespread and may concern 20 % of prescriptions in general practice. These prescriptions may

lead to serious public health issues and off-label drug use should be regularly monitored.
Aim: To evaluate if pharmacists represent a good partner for detecting off-label drug use.
Methods: We conducted a retrospective analysis of questions received by the regional pharmacovigilance centre of North of France (RPVC) from January 1st 2010 to December 31th 2014 that came from community and hospitals pharmacists and concerned off-label drug use (i.e. off-label indication, dosage, route of administration).
Results: During the study period, 4572 questions had been received by the RPVC, 58 of them concerned off-label drug use and were detected by pharmacists (i.e. 1.27 %). The number of questions increased during the study period: 8 in 2010, 7 in 2011, 10 in 2012, 14 in 2013 and 19 in 2014. Questions came mainly from community pharmacists (72.41 %). About one third of the questions concerned children. Off-label drug use was mainly related to off-label indication in 84.48 %, off-label dosage (8.62 %) and off-label route of administration (6.90 %). Drug involved were mainly drugs acting on the nervous system (21.74 %), drugs acting on the alimentary tract and metabolism (15.94 %), dermatologicals (11.59 %), drugs acting on the musculo-skeletal system (11.59 %) and drugs acting on the cardiovascular system (10.14 %).
Conclusion: Pharmacists are good sentinel for detecting off-label drug use. The number of questions related to off-label use has increased during the study period. It may be due to the successive sanitary problems of off-label drug use that happened in France: "Mediator scandal" in 2009, "Diane 35 affair" in 2012. Pharmacists, especially community pharmacists, should be more involved in off-label drug use detection, which can lead to serious public health problem.

P 056

Underreporting Adverse Drug Reactions (ADR) and Medication Errors (ME): a Problem in Hospital Pharmacovigilance

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Introduction: Pharmacovigilance programme is based in identifying the risks of adverse drugs reactions (ADR) associated with the use of drugs in order to enhance patient safety. Preventing medication errors (ME), making errors visible, and mitigating the effects of ME are also an important part of a pharmacovigilance programme.
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 ADRs and ME underreporting problem.
Methods: The study was conducted, from January to December 2014 and was based on an analysis of spontaneous ADRs and ME 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. A comparison with 2013 when several strategies were developed for increasing ADR and ME reporting was made.
Results: Twenty ADRs and 252 ME reports were registered in 2014 vs 51 and 349 in 2013. The highest ADR rate was found in the adult age group 25 to 50 years. The nurse team (90 %) reported the most ADRs in both years. The most noticeable ADRs occurred in skin tissues, with rashes being the most common reactions. The drugs responsible for most ADRs were paclitaxel, vancomycin and tramadol, 85 % of ADRs had moderate severity, thus requiring intervention. Most of the ME were in prescription and administration process (preparation process was the most common in 2013). The most common types of error throughout the medication process were, dose and omission of drug/dose. Educational activity, modification of ME reporting form, including computerized report, and implementation of a monitoring systems with feedback to the reporters were interventions developed during 2013 and an improvement in the number of ADRs and ME reports was observed in relation with 2012 reports however a decrease in both ADRs and ME reports was detected in 2014. A series of factors were considered responsible including knowledge, respondents' motivation, lack of time and physicians attitudes.
Conclusions: ADR and ME underreporting continues to be an important problem in hospital pharmacovigilance. More interventions should be designed for motivation and involvement of physicians to report ADRs and ensure safer drug use.

P 057

Adverse Drug Reactions Induced by Cotrimoxazole: Still a lot of Preventable Harm

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Introduction: Owing to its broad antimicrobial spectrum and low cost, cotrimoxazole is still largely prescribed. However, it is known to induce various adverse drug reactions (ADRs) that warrant to further pharmacovigilance monitoring and ensure rational prescribing.
Aim: Describe regional data on spontaneous reports on cotrimoxazole and assess the pertinence of prescription in patients who presented with ADRs
Methods: Cases of ADRs suspected to be induced by cotrimoxazole reported to the Bordeaux regional pharmacovigilance centre (France) between 1st January 2009 and 15th June 2014 were described. Seriousness of ADRs was assessed according to international pharmacovigilance definition. Pertinence of prescription was evaluated through two criteria: (1) respect of the summary of product characteristics (SmPC) in terms of posology, contra-indications, warnings and interactions and (2) pertinence of the indication. This criteria was evaluated with respect to clinical and biological parameters by an expert committee in clinical pharmacology, pharmacovigilance and infectious diseases in reference to the SmPC and recommendations of health authorities or scientific societies. Preventability of ADRs was assessed using an algorithm developed by the French pharmacovigilance centres.
Results: A total of 96 cases were analysed. Median age of patients was 61 years (range: 1-94) and 59.4 % were male. Almost two-thirds of patients (62.5 %) had at least one risk factor for cotrimoxazole use: 42.7 % were 65 years old or above, 17.7 % had an history of hematological disorders, 15.6 % kidney failure and 15.6 % diabetes. Cotrimoxazole was mostly prescribed for urinary tract infections (17.7 %), prophylaxis of opportunistic infections (15.6 %), osteitis (9.3 %) and

treatment of opportunistic infections (8.3 %). ADRs were most frequently skin disorders (45.8 %) and hematological disorders (22.9 %). More than half of ADRs (58.3 %) were serious (44.8 % leading to or prolonging hospitalization). In the majority of the cases (86.4 %), patients recovered or recovery was ongoing at the time of reporting. In 63.5 % of cases, at least one recommendation of the SmPC was not respected (12.5 % of non-assessable cases). Non respect was mostly due to combination with drugs inducing hyperkalemia (36.5 %), continuation of cotrimoxazole after the first signs of skin reaction (22.9 %) and a too long treatment duration (21.9 %). In 28.1 % of cases, the indication was considered as not pertinent (17.7 % of non-assessable cases) and half of the ADRs were classified as preventable or potentially preventable (28.1 % of non-assessable cases).

Conclusion: Prescribers should be encouraged to limit the prescription of cotrimoxazole to situations with no alternative and must be more aware of the risks of this old medicine.

P 058

Case-by-Case Assessment of ICSRs from Marketing Authorization Holders: A Pilot Study

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Introduction: Over the past years the number of Individual Case Safety Reports (ICSRs) from Marketing Authorization Holders (MAHs) received by the Netherlands Pharmacovigilance Centre Lareb has shown a steady increase. Since these reports can contain valuable information, their role in the signal detection process should be evaluated.

Aim: In this pilot study we investigated whether case-by-case assessment of ICSRs received from MAHs contributes to signal detection.

Methods: For two months all ICSRs received from MAHs through the Eudravigilance database were assessed independently and in duplicate by eight rotating pairs of assessors on a weekly basis. A custom made tool allowed for a quick assessment of the cases. Each assessor selected relevant ICSRs for the weekly signal detection meeting (SDM) as they would for ICSRs reported directly to Lareb by healthcare professionals and patients. At the SDM it was decided whether the association described in the ICSR should be analyzed in further detail. Subsequently, it was decided whether the association constituted a safety signal or not. Additionally, the inter-assessor agreement was used to determine the consensus for selection of reports between different assessors. The observed agreement (%) and Cohen's Kappa were used to determine the inter-assessor consensus.

Results: A total of 1750 ICSRs were assessed in two months. Of these, 94 (5.4 %) were selected for the SDM, and subsequently 14 (0.8 %) of them were selected for detailed analysis. The detailed analyses did not result in new safety signals. The observed inter-assessor agreement for all ICSRs was 90.4 % which was mainly due to agreement on reports not selected for the SDM (agreement reports not selected 88.8 %, agreement reports selected 1.6 %), whereas Cohen's kappa was 0.2.

Conclusion: Our pilot study showed that case-by-case analysis of MAH reports did not contribute to any new signals and is probably not the most appropriate method for signal detection of MAH reports, especially taking the time-consuming aspect into consideration. The lack of signals may partly be explained by the poor documentation level of most ICSRs and the large number of reports from patient support programs, which consisted of a rather homogeneous set of reported ADRs. This homogeneity also leads to repeated assessment of the same associations which could also be addressed using different methods, such as statistical screening. The low inter-assessor agreement can be partly explained by low prevalence of ICSRs selected for the SDM, as well as the subjective aspects that are inherent to signal detection.

P 059

A Medicines Regulatory Perspective on Women's Medicines

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The discipline of medicines regulation has been profoundly shaped and influenced by women's medicines. This presentation will give an overview of the key issues in regulation of medicines for women, from the early tragedies of thalidomide and diethylstilboestrol to very recent examples of regulatory action to protect women's health.

There are a number of special regulatory challenges relating to women's medicines and some interesting examples will be covered in this talk. Areas of interest include medicines in pregnancy, complimentary therapies for women's health, new medicines, oral contraceptives, access to women's medicines (including legal reclassification), use of medicines by healthy women and ongoing assessment of benefit versus risk.

The impact of regulation on women's medicines will also be discussed. Future prospects for regulating these important products include routine involvement of women in decisions which affect their health.

P 060

Analysis of UK Spontaneous Adverse Drug Reaction (ADR) Reports from the Yellow Card Scheme (YCS) from 2010 to 2014

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Introduction: The Yellow Card Scheme (YCS) is one of the most recognised spontaneous adverse drug reaction (ADR) reporting schemes worldwide and is an important means of monitoring drug safety in clinical practice to ensure that all medicines are acceptably safe, The evaluation of ADR reports identifies populations for which the MHRA can focus its strategy to strengthen direct reporting amongst specific reporter groups. Spontaneous suspected ADRs are reported directly on a voluntary basis by Healthcare Professionals (HCPs) and as of 2005 by patients via the Scheme. In 2008, an enhanced version of the Yellow Card web form was launched in to facilitate reporting with different forms for healthcare professionals and patients. The website was further updated in 2012 to provide an enhanced platform, supporting the requirements of the new pharmacovigilance legislation.

Aim: To analyse ADR data and identify areas to focus the Yellow Card strategy to strengthen reporting within the UK.
Method: We performed an analysis of spontaneous ADR reports received by the MHRA from 2010 to 2014. All drugs were analysed by active substance using the MHRA's drug dictionary and suspected ADRs were classified using Medical Dictionary for Regulatory affairs (MedDRA).
Results: 2014 has seen a 36 % increase in the number of ADR reports received compared to 2010 and a 2 % increase from 2013 to 2014. In 2014, the number of Yellow Card reports received from patients form 22 % of all reports directly received by the MHRA whilst HCP reports account for 46 %.2014 has seen a 12.8 % increase in electronic reporting compared to 2013 and electronic patient reports have increased from 73 % in 2010 to 88 % in 2014 whilst electronic HCP reporting increased from 38 % in 2010 to 79 %. The largest proportion of reports was received from GPs (28 %) and the number of reports from nurses fluctuated during 2010–2014 due to various vaccination campaigns.
Conclusion: The data highlights the importance of both regular targeted promotional activities to raise awareness of the Yellow Card Scheme, and making ADR reporting as quick, easy and accessible as possible. Continued engagement with HCPs and patients is key to maintaining the success of schemes such as the YCS as well as effective monitoring and communication of drug safety issues.

P 061

A Follow-Up Questionnaire: A Successful Tool to Study Topics Related to Packaging Changes of the Drug Thyrax® in the Netherlands

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Introduction: The drug Thyrax® (levothyroxine) is indicated for the treatment of hypothyroidism. In December 2013 the packaging of Thyrax® changed from bottle to blister in the Netherlands. The Marketing Authorization Holder introduced this with a patient flyer. In October 2014 the Netherlands Pharmacovigilance Centre Lareb had received over 80 reports of adverse drug reactions (ADRs) associated with this packaging change. About 50 % of the reports mentioned reactions which match symptoms of hyperthyroidism, like palpitations, hyperhidrosis and jitteriness. The Dutch Medicines Evaluation Board was informed about these findings leading to a Direct Healthcare Professional Communication to inform physicians and pharmacist about a possible dosage increase of levothyroxine after switch from bottles to blisters. In February 2015 various media addressed this issue resulting in about 1800 reports concerning ADRs that occurred after this packaging change. Over 90 % of these reports came from patients.
Aim: To study communication regarding the Thyrax® packaging change and its impact on the health care system.
Method: An electronic follow-up questionnaire was sent out to all patients who reported ADRs associated with the packaging change.
Results: The overall response was 73 %. Only 4 % of the respondents was informed in advance about the packaging change. 74 % of the respondents mentioned they had no concerns about a possible change in effect: "I didn't even think about a possible influence of the packaging on ADRs" and "I had no idea this could affect the therapeutic effect". Most of the patients (47 %) thought of a relation between the packaging change and ADRs after media covered this issue: "It was on the news and on the television show 'Radar' there was a woman who had the same complaints I had". As a result of the ADRs most respondents used extra health care, which included at least one extra visit to the general practitioner (79.1 %), specialist doctor (54.5 %) or pharmacy (57.6 %). 85.3 % of the respondents had extra blood tests to determine thyroid levels.
Conclusion: Patients who reported ADRs concerning the Thyrax® packaging change are willing to provide extra information. The questionnaire showed that media attention was necessary for patient to relate their ADRs to the packaging change. For the responders of this questionnaire, the packaging change resulted in an increase in use of health care. Since only patients who experienced ADRs reported to Lareb, this analysis should not be generalized to the Thyrax® packaging change in general. However, it gives an idea of what impact a drug packaging may have.

P 062

Seasonal and Geographic Variation In Adverse Event Reporting

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Introduction: A number of illnesses demonstrate seasonal variations. Pharmacovigilance is unique among public-health surveillance systems in terms of the clinical and quantitative variety of medical illnesses under surveillance.
Aim: Using a large health-authority drug-safety database comprised of spontaneously reported adverse events (ADEs), we assessed whether a set of illnesses that might be expected to display seasonality in general, did so when the illness was reported as a suspected adverse drug reaction.
Methodology: For this preliminary investigation of the seasonality of illnesses reported as ADEs, we studied data from the US FDA Adverse Event Reporting System (FAERs). A convenience sample of AEs was classified into one of three subsets: one containing AEs expected to be associated with warmer and/or sunnier seasons: photosensitivity reaction, heat exhaustion, heat stroke, and sunburn; one containing AEs expected to be associated with colder seasons: hypothermia and Raynaud's phenomenon; and one in which some data/experience suggests seasonality but for which there was no clear expectation/pre-existing rationale for seasonality: anencephaly and interstitial lung disease. We analysed global data as well as geographic strata corresponding to the United States, Japan, and Scandinavia. Geography-stratified analysis was performed to explore for possible interactions between seasonality and geography, and to provide some internal control comparisons. Seasonality was assessed using a statistical procedure based on a physicogeometric setting that leads to a test statistic involving sine and cosine functions. The method is reminiscent of finite Fourier analysis. This procedure can detect sinusoidal and other types of variation.
Results: The following AEs displayed statistically significant seasonal reporting patterns either globally and/or in one/more geographic areas: hypothermia, photosensitivity reaction in Japan, heat exhaustion, heat stroke, and interstitial lung disease (annual sinusoidal); photosensitivity

reaction in the USA (semi-annual sinusoidal); and sunburn (hybrid annual sinusoidal and U-shaped model). The following AEs failed to demonstrate seasonal reporting patterns: Raynaud's phenomenon and anencephaly. When sufficient data were available for all three regions, the occurrence of spontaneous-reporting seasonality was a function of the geographic area for hypothermia, photosensitivity reaction, and interstitial lung disease.
Conclusions: Understanding seasonality of AE-reporting may have public-health implications both with respect to public-health educational interventions and in mitigating false-positive pharmacovigilance signals. A more systematic study of the seasonality of spontaneous AE reporting, including additional events with more/less biological rationale for seasonality, may uncover previously unexpected reporting patterns.
Keywords: Drug safety; Geographic variation; Pharmacovigilance; Public health; Seasonality; Spontaneously reported adverse events

P 063

Potentially Inappropriate Prescribing and the Risk of Adverse Drug Reactions in the Elderly Swedish Population

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Background: Potentially inappropriate prescribing (PIP) criteria are widely used for evaluating the quality of prescribing of elderly. However, there is limited evidence on their association with adverse drug reactions (ADRs) across healthcare settings.
Objective: To determine the prevalence of PIPs, defined by the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria, in the Swedish elderly general population, and to study the association between PIPs and occurrence of ADRs.
Method: We identified 813 persons ≥65 years old from a random sample of 5025 adults drawn from the Swedish Total Population Register. A retrospective cohort study was conducted among elderly with healthcare encounters in primary and specialised healthcare settings during a three-month period in 2008. PIPs were identified from the Swedish Prescribed Drug Register, medical records and health administrative data. ADRs were independently identified by expert reviewers in a stepwise manner using the Howard criteria.
Results: Overall 374 persons had ≥1 PIPs and 159 experienced ≥1 ADRs during the study period. In total, 29.8 % of all ADRs was caused by PIPs. Persons prescribed PIPs had twofold increased odds of experiencing ADRs (OR 2.47; 95 % CI 1.65–3.69). PIPs potentially caused 60.0 % of vascular and 50.0 % of nervous systems disorders. Moreover, 62.5 % of falls were potentially caused by PIPs.
Conclusion: PIPs are common among the Swedish elderly and are associated with increased odds of experiencing ADRs. Thus, interventions to decrease PIPs may contribute to preventing ADRs, in particular ADRs associated with nervous and vascular disorders.

P 064

Trends of Drug-Safety Alerts from 2002 to 2014: Data from Portugal

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Introduction: Before marketing authorization pre-clinic and clinic studies are performed to study the efficacy and safety of new drugs. However unknown Adverse Drug Reactions (ADRs) can arise during the post-marketing authorization [1, 2]. Spontaneous reporting of ADRs and the safety alerts generated placed an important role on acknowledge about drugs safety and consequently on the safety of patients.
Aim: To evaluate all safety alerts published by Portuguese National Health Authority (INFARMED), between 2012 and 2014.
Methods: An observational study. All safety alerts published in the webpage of INFARMED were analysed and the following data were extracted: active substance name (classified according to ATC code), the event that led to the alert and safety measures adopted.
Results: 304 safety alerts were included in the study. The ATC group with most alerts were M—Musculo-skeletal system (n = 53), N—Nervous system (n = 42) and B—Blood and blood forming organs (n = 34). Statistical significant correlation was found between time and alert publications for four ATC groups.
Conclusion: Yearly are published several safety alerts, being same of that relative to drugs that are in the market for many years ago. This highlights the importance of pharmacovigilance system to protect patients from drug adverse events.
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P 065

Impact of Co-Payments for Primary Care Services in Antibiotic Use: A Time-Series Analysis

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Introduction: Health systems economic sustainability is a major concern worldwide. Accordingly, the increase of National Health System overall moderating fees (co-payments) to moderate the access has been adopted in countries as Portugal to diminish healthcare costs. However, health policies have unclear effects on the clinical practice, namely on the use of antibiotics [1].

Aim: To evaluate the impact of co-payments on antibiotic quality prescription and consumption.

Methods: We performed a retrospective observational study of the antibiotic prescription in public primary care facilities and the overall antibiotic consumption from 2010 to 2014. The quality of antibiotic prescribing was assessed through the quality indicators validated by Coenen et al (2007) [2] and yearly published by ESAC-European Surveillance for Antibiotic Consumption network. In Portugal, the co-payments in NHS primary care facilities were applied to services as general practitioner consultation, nurse consultation, consultation at home, consultation without the presence of the patient and primary care emergency department consultation in January 1st, 2012. Differences after implementation of the new co-payments fees were evaluated using segmented regression analysis (values significant: $p < 0.05$) [3]. Short and long-term coefficients were calculated (95 % confidence interval for the coefficients). The model was adjusted for the seasonal variation of antibiotic use.

Results: Statistical significant long-term decreasing was found on the overall rate of antibiotic prescription in the public health system, measured in number of packages per 1000 inhabitants per day (PID) and in defined daily doses per 1000 inhabitants per day (DID); however, in the case of antibiotic consumption, a tendency for increasing was found for long-term effect of the co-payments.

Conclusions: Our results revealed that (i) overall antibiotic prescription in public primary care facilities has decreased and overall antibiotic consumption seems to maintain or increase. The results highlight the importance of measuring the real impact of health policies on medicines use and population health.

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P 066

Analysis of Records from Embase/Medline/IPA Databases (STN International) from the Point of View of Pharmacovigilance

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Introduction: The European Medicines Agency (EMA) prepares to launch the new medical literature monitoring service (MLM) comprising monitoring of selected medical literature for reports of suspected adverse reactions containing certain active substances. As of the 1st July 2015, the service will cover the top 50 active substance groups. It is important to watch, follow and evaluate reliability of the service and information sources in the initial phase of processing. Medistyl Prague is competent and ready to realize such evaluation with regard to many years' experience with Embase/Medline/IPA databases and monitoring of local journals.

Aim: To evaluate the reliability, completeness and flexibility of information sources selected for the new medical literature monitoring service.

Methods: Records from Embase/Medline/IPA databases accessible in STN International database network are analysed from the point of view of requirements of Good Pharmacovigilance Practices guideline—structure, completeness and complexity of keywords, controlled terms and other descriptors and thesauri is evaluated with regard to pharmacovigilance. The searching results from Embase/Medline/IPA databases are compared with the reports from local journals monitoring in countries of Central and Eastern Europe that is realized by reading and subsequent processing of full text articles. Coverage of journal titles from Central and Eastern Europe in worldwide databases is evaluated. Flexibility and swiftness of different methods and approaches are compared.

Results: The evaluation comes out from long-term usage and assessment of above mentioned databases and it will be completed and quantified by the "hot topical" analysis, carried out in July–September 2015, after launching of the first phase of medical literature monitoring service by EMA.

Conclusions: The conclusions will be specified and quantified after analysis, carried out in July–September 2015 and expressed as a high topical opinion shortly before the presentation.

P 067

Desloratadine and Aggressive Reaction Reported in VigiBase

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Introduction: Signal detection in the WHO Global Individual Case Safety Reports database, VigiBase®, applying vigiRank 1, identified a potential safety signal for desloratadine reported with aggressive reaction. Desloratadine is a selective peripheral histamine (H1) receptor antagonist, indicated for the relief of symptoms of allergic rhinitis and urticaria in children and adults. Psychiatric and nervous system disorder reactions, including hallucinations, psychomotor hyperactivity and seizures, have been reported with desloratadine during the post-marketing period 2, 3. In clinical trials, emotional lability was reported at greater frequency for desloratadine than for placebo in children 12–23 months of age 3.

Aim: To explore a possible causal relationship between desloratadine and aggressive reaction.

Methods: Clinical assessment of reports with desloratadine and the WHO–ART preferred term 'aggressive reaction' retrieved from VigiBase with data up to March 2015.

Results: At the time of assessment, VigiBase included 17 reports of desloratadine reported with aggressive reaction. The reports originated from 10 countries in Europe and North America and represented 6 females and 11 males. Ten reports involved children or adolescents, of which eight were 8 years of age or younger. The paediatric reports represented eight cases with plausible time to onset: seven cases within a few days and one

case within a few weeks. Six of these reports described that the patient had recovered or was recovering upon withdrawal of the drug, and of these, two reported a subsequent positive rechallenge. Desloratadine was the sole suspect drug in nine of the paediatric reports, whereof five had no concomitant medication reported. Half of the paediatric cases reported a higher than recommended daily dose of desloratadine. One of the adult reports presented no obvious confounders, a rapid onset of the reaction, a positive dechallenge, and a positive rechallenge. The remaining adult reports presented with confounders or were poorly documented.

Conclusion: Reports in VigiBase support a possible causal relationship between desloratadine and aggressive reaction, particularly in children. The paediatric reports represent a suggestive temporal relationship, positive de-and rechallenges, and only few identified possible confounders. Previous reports of central nervous system effects from desloratadine, including emotional lability in children, further support this assessment.

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P 068

A Signal based on Spontaneous Reports of Atomoxetine and Neutropenia in Paediatric Patients

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Introduction: The WHO Global Individual Case Safety Reports Database, VigiBase® contains nearly 11 million reports and the data is routinely analyzed to detect signals of adverse drug reactions. In September 2014, Uppsala Monitoring Centre performed signal detection targeted at the pediatric population. This activity identified a case series of neutropenia with atomoxetine, an inhibitor of the presynaptic noradrenaline transporter, indicated for the treatment of Attention-Deficit/Hyperactivity Disorder [1]. A literature review identified no reports of neutropenia in association with atomoxetine.

Aim: Exploring the evidence for a causal link between atomoxetine and neutropenia in paediatric patients.

Methods: Case-by-case assessment of relevant reports in VigiBase up to February 2015.

Results: There were 33 unique reports of neutropenia in association with atomoxetine in VigiBase, of which 25 cases concerned children and adolescents. The reports were submitted from seven countries. The patients' age ranged from 6 to 17 years (median 12 years). There were 23 males and 2 females. Atomoxetine was the only drug suspected in 20 of the 25 cases. In three of the remaining cases, there were co-suspected drugs for which neutropenia is labelled. Concomitant drugs were reported in 10 of the 25 cases. Time to onset was reported in 11 cases and ranged from 14 days to 10 months (median 50 days) with five cases between 14 and 27 days. In the 10 cases where recovery was reported, the drug was withdrawn in seven, the dose was increased in one and the fate of the drug was unknown in the remaining two. In the five cases where the patient had not recovered, the drug had been discontinued in four and the fate of the drug was unknown in the remaining case.

Conclusion: Case reports in VigiBase suggest that there is a signal for the association of atomoxetine and neutropenia. The time to onset between 14 and 27 days in five cases is consistent with drug-induced neutropenia. The seven cases with a positive dechallenge are supportive of a drug-induced effect. The possible association appears predominantly in the paediatric population. Twenty-five (76 %) out of all 33 cases of atomoxetine and neutropenia were reported in the children and adolescent age groups, compared to overall reporting in VigiBase which indicates that of the 16,504 atomoxetine reports submitted, the age group from 2 to 17 years represents 60 % of the total reports.

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P 069

Angiotensin-Converting-Enzyme Inhibitors Induced Cough: Diagnosis and Management by 1100 French-Speaking GPs

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Introduction: Cough may appear in more than 11 % patients treated by ACE-inhibitors (Angiotensin Converting Enzyme inhibitors)

Materials and methods: an electronic questionnaire was send to the 3rd quarter 2014 to 14,893 french-speaking GPs (Belgium, Canada, France, Switzerland). The theme was indicated that the management of a cough. A clinical vignette involved a cough in a patient treated with ACE inhibitors was presented and secondary questions specifically relating to the ACE inhibitor-induced cough were proposed.

Results: Among the 1100 GPs respondents, 690 (62 %) were employed in France, 162 (15 %) in Belgium, 140 (13 %) in Switzerland and 108 (10 %) in Canada. The demographic characteristics of respondents were similar to those of the GPs population in each country. Based on the clinical information provided in the vignette, 92 % of physicians immediately evoked an ACE inhibitors induced cough. Other diagnosis discussed differed between countries (whooping cough in France, respiratory diseases in Canada). Once given the normality of all additional tests, 71 % of physicians diagnosed a cough induced by ACE inhibitors and 67 % proposed antihypertensive therapy change. If the risk factors of ACE inhibitors cough were not known, management was appropriate. However this diagnosis was considered difficult by 26 % of respondents. Only

5.09 % of GPs said they had already reported this side effect to a pharmacovigilance centre.

Conclusion: Clinical vignette showed the diagnostic difficulty of ACE inhibitor-induced cough, even though the management is well known by GPs. An awareness of pharmacovigilance might be possible to avoid frequent diagnostic delay.

P 070

Spontaneous Reporting by Patients: Sociodemographic and Economic Factors that Promote Reporting

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Introduction: Adverse drug reactions (ADRs) are a common and an important cause of morbidity and mortality. They bring a significant economic and social impact. Drug safety monitoring is mostly performed on a voluntary basis by healthcare professionals through spontaneous reporting systems (SRS). The SRS suffer from several problems, among which selective reporting and under-reporting [1, 2]. In order to overcome this, direct patient reporting was recently introduced.

Aim: To identify which health, social, economic, cultural and population-related factors might explain spontaneous reporting rates of ADRs by patients.

Methods: Several global demographic and socioeconomic indicators from 50 countries participating in the WHO International Drug Monitoring were retrieved. The data derived from databases maintained by a number of national and international organizations. After the collection of relevant data, a statistical model was built. Using methods of univariate logistic regression, indicators that had a significant association with the variable for patient reporting were selected. A multivariate logistic regression method was developed, relating reporting level with different indicators. These and descriptive statistics were performed using R-CRAN version 3.2.0.

Results: Of the 50 countries, 14 show a significant reporting level. For the analysed indicators, though several showed an association with the reporting level, the indicator "Health Expenditure" is enough to explain a higher ADR reporting rate by patients (OR = 2.01 with 95 % CI:1.3–3.12). The statistical model showed an area under the curve (AUC) of 0.80, which is accepted as a good discriminative capacity [3].

Conclusion: This study identified several indicators that are directly influencing a higher reporting rate of ADRs by patients. However, health expenditure alone is enough to explain a higher reporting. Although a "gross" indicator and knowing the health policies should address citizens participation, the present results showed that frail societies are those having less return from patient involvement to the overall therapeutic quality.

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P 071

Strengthening Capabilities for Benefit Risk Assessment in Post-Marketing—The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action

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Introduction: The legislation on pharmacovigilance that came into force in July 2012 [1] includes a number of provisions to strengthen the post authorization follow-up of medicinal products throughout their life cycle. The continued benefit/risk (B/R) assessment of medicines is a cornerstone for the effective operation of the pharmacovigilance (PV) system in the European Union (EU). Improving assessor skills and consistency of procedures in Member States is one of the most important aspects of pharmacovigilance legislation implementation.

Aim: To explore the new and existing standards and tools for assessment and propose a training program to build-up competences in national competent authorities (NCA) to effectively address B/R assessment of medicines.

Methods and Results: The WP8 (lifecycle pharmacovigilance) web-based surveys were conducted from July to November 2014 in 28 NCAs participating in SCOPE. 25 of the 28 NCAs completed the survey (response rate of 90 %). The surveys assessed current practices in RMP, PASS, PSUR/PSUSA and referral assessment with a focus on good PV practice, useful tools, B/R assessment challenges and possible solutions. The results of the 3 different surveys have been summarized by descriptive statistics. The information collected in the surveys will be used to make recommendations for subsequent training of assessors. Some areas were difficult to explore due to a limited experience so far (e.g. assessment of the need for PAES and study designs to test the effectiveness of additional RMMs). The areas where more guidance is needed have also been identified (e.g. some aspects in the context of referral, PSUSA etc.). The availability of further guidance and tools (e.g. checklists/"hint and tips" documents) to facilitate the assessment was considered beneficial by NCAs. On the basis of NCAs input, a list of recommendations for trainings and useful literature was created for the continued education of PV assessors. An effort has also been made to identify and characterize the most appropriate alternative data sources (outside spontaneous reporting)

available in European NCAs in order to share a common approach regarding their use.
Conclusions: A collaborative approach, proposed in the SCOPE, and recommendations based on the survey results will lead to improvement in understanding and in developing solutions for the different challenges faced by NCAs during the B/R assessment and will help promotion of good pharmacovigilance practice (e.g. identification of most useful tools).
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P 072

Intensive Monitoring of Adverse Drug Reactions—State of the Art

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Introduction: It is well known that information on medicines safety, gathered in clinical trials, is insufficient when the medicine enters the market. From the early sixties the scientific community searches for the best practices in pharmacovigilance. The goal is to collect useful information of Adverse Drug Reactions (ADRs) as early as possible. Risk minimisation measures are interventions intended to prevent or reduce the occurrence of ADRs and to reduce their severity or impact on the patient. Active pharmacovigilance, like intensive monitoring, has been performed by different organisations and prove validity to generate signals in an early stage.
Aim: To highlight the scientific research on intensive monitoring of ADR and to review the reasons to include active substances in the list under additional monitoring of European Medicines Agency.
Methods: A systematic review based on peer-reviewed articles, published between 2000 and 2014, was performed in PubMed and for primary search were used mesh terms as (methods in pharmacovigilance OR pharmacovigilance strategies) AND (intensive monitoring of adverse drug reaction) AND (educational tool in pharmacovigilance) AND (patient reporting). The list of medicinal products under additional monitoring (May 2015) and the Guideline on good pharmacovigilance practices (modules VI and XVI) were included in this review.
Results: 32 articles were retrieved from the search. 3 Centre's worldwide where intensive monitoring studies are performed, were identified, namely the LIM-Lareb Intensive Monitoring (The Netherlands), the PEM-Prescription Event Monitoring (UK) and the IMMP-Intensive Medicines Monitoring Programme (New Zealand). Was checked the reasons to include an active substance in the list of medicinal products under additional monitoring and quantified each active substance per reason. We also identified the pharmacotherapeutic groups by ATC code of active substances included in the list.
In opposition to spontaneous reporting, intensive monitoring programs usually focus on one medicine and unlike clinical trials in an intensive monitoring study it is possible to include all patients, without the exclusion criteria that limit the coverage of real individual characteristics of medicines consumers in clinical trials.
Conclusion: Intensive Monitoring confirmed to be a potential important method in post-marketing medicines surveillance. It can anticipate information about severe or unexpected ADR's. It gives real information temporally linked with the adverse reaction and allows an early identification of adverse events of medicines. In the future intensive monitoring should be considered to be used as an educational tool for patient reporting.

P 073

Fatal Risk Assessment of Use of Fluconazole During Pregnancy

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Introduction: Fluconazole is a synthetic bis-triazole antifungal effective and well tolerated widely used to treat fungal infections. Evidence suggests that fluconazole displays a dose-dependent teratogenic effect, yet its administration appears to be safe at lower doses (150 mg/day) during pregnancy. Due to the rarity of teratogenic events, the occurrence of a distinct and single pattern of malformations associated with the exposure to fluconazole during pregnancy suggests some causal relationship.
Aim: To survey the available information in order to understand the safety profile and the teratogenic impact of fluconazole administered during pregnancy.
Methods: Was carried out a comprehensive review of available literature, published between 1996 and 2013. The information was gathered from electronic databases such as Medline, using mesh terms as (pregnant women OR pregnancy) AND (fluconazole) AND (birth defects OR pregnancy outcome OR teratogenesis OR embryopathy OR congenital anomalies) without any filter. Of the 60 articles retrieved, eight were review articles and have not been found randomized controlled clinical trials. In the absence of better evidence, it was considered down the pyramid of evidence for other types of studies, particularly cohort studies and case reports.
Results: During the research in bibliographic systems was not always possible to find the best level of evidence. The cohort studies and case reports were critically analysed for the occurrence of a distinct and single pattern of malformations. The similarity of congenital malformations described in the clinical case reports suggest that the teratogenic effect of fluconazole at high doses causes a characteristic pattern of craniofacial, skeletal and cardiac malformations. Cohort studies have failed to show evidence of an association between exposure to fluconazole and the specific effects linked to teratogenicity of fluconazole. Surprisingly few cohort studies have shown the prevalence of statistically significant risk to cardio toxic effects.
Conclusions: The decision to treat a woman with fluconazole in early pregnancy remains a complex problem. Due to the rarity of teratogenic fluconazole events, especially with regard to cardio toxic abnormalities, more large-scale epidemiological studies are needed to determine the

effective risk of prevalence of specific birth defects from exposure to fluconazole during pregnancy.

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P 074

Assessment of Risk Perception of ADR by Patient's—Pilot Study

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Introduction: Aside from its benefits, every drug also possesses inherent risks. Several studies have shown that many adverse drug reactions (ADR's) could be avoided, if patients were more aware of their medicine's risks. Drug labels' contain fundamental information to patients, who ponder all the risks and benefits, but despite this, information is sometimes incomplete or difficult to understand and assimilate by patients. This highlight the importance of perception risks studies in real populations.
Aim: To characterize how ADR risks' are perceived by patients and to assess the level of knowledge of the ADRs national reporting system.
Material and Methods: Was performed a observational cross-sectional study, based on a questionnaire hetero-administered, with 27 questions divided into 3 groups The study was conducted in a primary healthcare centre in Coimbra, Portugal. During two months, a total of 91 patients were asked to participate in this study, under informed consent. In order to evaluate risk perception and assess the knowledge of the ADRs reporting system, 5 questions were selected and to each answer a value was attributed (0; 0.5; 1). When added all the answers, the final value was corresponded to either a positive (≥ 2.5) or negative (< 2.5) perception.
Results: In our sample 74.7 % ($n = 68$) were taking drugs, and 54.4 % ($n = 37$) claimed to know their side effects. The study had shown that risk perception was undeniably low amongst patients, with a rate of 85.7 % of negative responses. Only 17.6 % ($n = 16$) recognized the Portuguese Pharmacovigilance System, in spite of the evident (93.4 %; $n = 85$) wish to learn more about the reporting procedure. In addition, nearly all patients, who had previously experienced an ADR, preferred to report this event to a physician and only 5 reported it to National Pharmacovigilance Centre. Alternatively, they chose to report the event to their physician (61.1 %; $n = 22$), pharmacist/pharmacy technician (5.6 %; $n = 2$) or not to inform at all (33.3 %; $n = 12$). Most of the patients still believe in the unconditional safety and efficiency of every medicine and its risks aren't even questioned and they falsely consider prescription drugs more trustworthy.
Conclusion: In this study patients, demonstrated a poor level of knowledge regarding drug's safety issues, hence the broad negative awareness. The low perception evidenced could influence negatively the relation with medicines. As a final conclusion, there is evident need to intervene in order to educate patients about the importance of reporting a suspected ADR and how to do it.

P 075

Fatal Interaction Between Fusidic Acid and Pravastatin

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Introduction: Myalgia, cramps and elevated creatine phosphokinase (CPK) are common side effects observed with statins. Risk factors have been associated with these effects: age over 70 years, renal failure and/or liver failure, intensive practice of sport, high dosage of statins or such drug combinations.
Aim: To report a fatal case of rhabdomyolysis and acute renal failure in a patient treated with fusidic acid and pravastatin.
Case report: This case concerns a 67 year-old male patient, with a medical history of atrial fibrillation, high blood pressure and hypercholesterolemia. He was treated with pravastatin (40 mg per day) since 2007. In February, 2014, he was treated with fusidic acid (500 mg twice a day) in a context of a methicillin-sensitive Staphylococcus aureus infection. Ten days after the beginning of antibiotherapy, laboratory tests revealed a renal failure. The patient was hospitalised six days later: pravastatin treatment is stopped and fusidic acid treatment is continued. Nine days after the admission, rhabdomyolysis (confirmed by muscle biopsy) is highlighted with CPK level at 4587 IU/L (normal values: 15–130 IU/L). The patient's condition has worsened with multiple organ failure and the patient died a few days later. The latest values of CPK were 160,000 IU/L.
Discussion: In 2011, the Medicine and Healthcare products Regulatory Agency (MHRA) advised not to use oral fusidic acid with statins since an increasing numbers and severity of rhabdomyolysis cases occurring in this context. In the literature, there are 28 cases (including 8 fatal outcomes) of rhabdomyolysis in the context of co-prescription of these drugs. In these cases, statins predominantly suspected were atorvastatin and simvastatin, suggesting a mechanism involving the inhibition of CYP 3A4 isoenzyme, since these statins being metabolised by this route. However, cases with rosuvastatin (partially metabolised by CYP2C9 isoenyme) and our case with pravastatin (wich is not metabolised by cytochrome p450 enzymes) can't be explained by this hypothesis. Some authors suggest a competition between statins and fusidic acid in the hepatic glucuronidation of these two molecules. To our knowledge, this is the first published case with pravastatin, suggesting that rhabdomyolysis involving statins and fusidic acid interaction is a class effect. In France, prescription of fusidic acid is contra-indicated with HMG-coA reductase regardless of fusidic acid indication (cutaneous and osteoarticular infections) since January, 2015. Prescribers and pharmacists should be alerted about the risk of occurrence of severe complications or death with co-prescriptions of these drugs.

P 076

Risk of Extravasation Injury with PEDIAVEN and Other Parenteral Nutritions Used with Peripheral Intravenous in French Neonatal Intensive Care Unit

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Introduction: A severe case of extravasation from a peripheral vein infusion (PVI) of PEDIAVEN occurred in the neonatal intensive care unit (NICU) of ANGERS University Hospital. It resulted in skin necrosis which required a skin graft.
Aim: Following this case, we wanted to compare the practices of peripheral parenteral nutrition (PN) between the French NICUs.
Method: A questionnaire was sent to all French NICUs to assess their practices. Data collected were: type of PN, indications, frequency of extravasation in a year and consequences of extravasation.
Results 43 NICUs responded. 21 used PEDIAVEN and other PN, 4 used exclusively PEDIAVEN and 9 used exclusively other PN. 19 prescribed a PVI of PEDIAVEN versus 12 for other peripheral PN. Extravasation occurred in 12 NICUs (63 %) using PEDIAVEN versus 9 (75 %) with other peripheral PN. This side effect occurred 1–5 times/year regardless of parenteral nutrition. An inflammatory reaction was observed in 6 NICUs with a peripheral vein infusion of PEDIAVEN versus 8 with other peripheral PN. A skin necrosis was observed in 8 NICUs with a PVI of PEDIAVEN versus 6 with other peripheral PN.
Conclusion: The risk of extravasation from peripheral intravenous exists in the newborn, regardless of the solute used (PEDIAVEN or other PN) and the outcome is usually spontaneously favourable evolution. To our knowledge, no case-report with PEDIAVEN is described in the literature but several studies showed that PN prone to extravasation injury [1]. In the French National Database, 31 extravasations were described with a PVI of PEDIAVEN whose 4 with led to skin graft and 1 to a surgery. Tissue damage occurs as a result of differences in physiochemical characteristics, including pH and osmolarity, between the extravasate substance and the host tissue [1]. Regarding the osmolarity tolerated for a PVI, the data in the literature are conflicting [2]. There is no consensus on the osmolality threshold. Peripheral NP are better tolerated if the pH is between 6.5 and 9 [3] (PEDIAVEN 3.8 $<$ pH $>$ 6.5). Increased local monitoring for peripheral PN is necessary and removal of the infusion are is imperative in doubt.

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P 077

Delayed Iodinated Contrast Media Hypersensitivity After Coronary Angiography

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Introduction: Iodinated contrast media (ICM) used in coronary angiography (CAG) can induce both immediate and delayed hypersensitivity reactions. However, studies on delayed hypersensitivity reactions to ICM are relatively few and the reported incidence varies greatly.
Aim: To investigate the incidence and clinical features of ICM-induced delayed hypersensitivity reactions following CAG.
Methods: We prospectively monitored ICM-induced delayed hypersensitivity in patients who underwent CAG from February 2015 to May 2015 at the Seoul National University Hospital. The ICM agents used in the study were iodixanol and iopamidol. Symptoms were monitored from one hour to three weeks after completion of CAG.
Results: A total 265 cases of CAG was performed. Mean age was 63.6 years old and 70.5 % were male. Thirty five patients (13.2 %) were diagnosed as ICM-induced delayed hypersensitivity. In terms of onset, 23 patients (65.7 %) experienced symptoms within 3 days after the dye was injected during CAG ($<$24 h: 7 patients, 24–48 h: 7 patients, 48–72 h: 9 patients, $>$ 72 h: 12 patients). Skin symptoms were found in 88.6 % of patients who experienced delayed reactions and most of them were maculopapular eruption (88.5 %) and mild reactions involving $<$25 % of body surface (87 %). Mild chest discomfort and gastrointestinal symptoms such as nausea, vomiting, and dyspepsia were also reported in 0.75 % of the study subjects, respectively. There was no difference in incidence and clinical manifestations according to the individual contrast media used in CAG.
Conclusions: The incidence proportion of delayed hypersensitivity reactions to ICM was relatively high up to 13.2 % and most of them were mild skin rash.

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P 078

Better Knowledge Access for Capacity Building of Community Midwives to Reduce Maternal Morbidity And Mortality: Use of ICT

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Introduction: Pakistan stands disappointingly in line with other developing countries with high maternal and child mortality rates. More than 50 % of all maternal deaths occur in 6 countries. With only 8 doctors/10,000 and 5.6 midwives/10,000 only a quarter of pregnant women undergo a minimum of 4 antenatal visits. It is now been contended that providing optimal care to these women by conventional methods of western standards will take huge resources in terms of man power and finances. Focus is to train a community midwife with inbuilt connectivity with her community. Increasingly ICT has been used to facilitate training and skill development of local health workers. According to PTA Pakistan

has tele-density of 78 %, one of the highest in the region. Current work is preliminary data from a program of using ICT in capacity building of front line soldiers in urban slums in Karachi.
Aims: To assess ICT usage amongst community midwives and landscape analysis.
Methods: This work is being carried out under the umbrella of Midwifery Association of Pakistan (MAP) with a membership mounting to a thousand workers across Pakistan. As a part of landscape analysis as well as initiative of CME, we are holding a series of workshops and lectures to introduce them to ehealth and mHealth potentials in their connectivity to nearby better equipped centres in cases of emergencies.
Results: The results, so far reveal that mobile phone is owned by 97 % workers (all female). 98 % pay their phone bill. Type of phones ranged from basic to a smart phone. Majority used phone for sms and phone calls. Very few used it for web browsing and downloading educational materials (less than 5 %). Many have used Skype and social media (14 %). This trend was reflected in younger workers. 81 % have used mobile phone to contact nearest hospital. However, around 50 % used them to advise patients on antenatal, postnatal or neonatal care and immunisation. Only 1/3rd had access to internet. Only 9 % had used any kind of health app. Overwhelming majority showed willingness to be part of training program in eHealth (86 %). 100 % had electricity in their areas but power failures ranged from 2–10 h during the day and up to 4 h at night. Only 1/3rd had access to alternative power generation during these hours. This project is ongoing and we witnessed great enthusiasm amongst the participants. We acknowledge their contribution in the community and see a great potential in use of technology in strengthening their skills and capabilities.

P 079

Pilot Project of Recording and Assessing Medication Errors Within the German Spontaneous Reporting System

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Introduction: Up to 10 %of hospital admissions are due to adverse drug reactions and 20 % of these are preventable medication errors [1]. As a consequence of the new Pharmacovigilance legislation member states of the European Union (EU) are required also to record adverse reactions attributed to medication errors [2].
The Drug Commission of the German Medical Association (DCGMA) is currently developing a system for recording and assessing medication errors reported spontaneously by physicians. The project is funded by the Federal Ministry of Health and carried out in close collaboration with the Federal Institute for Drugs and Medical Devices (BfArM).
Aims: To evaluate

- the feasibility of a systematic analysis of medication errors within the existing structures of the German spontaneous reporting system;
- whether the information is suitable to deduce risk factors and intervention strategies.

Methods: Medication errors will be recorded that have caused harm to the patient. The existing spontaneous reporting form was revised to cover relevant information (e.g. type of medication error, stage of medication process). Following the "Good practice guide on recording, coding, reporting and assessment of medication errors-draft" of the European Medicines Agency [3] MedDRA codes are used as far as possible. The case reports are assessed within the structures of DCGMA and coded in a format, in which they can be forwarded to national and international institutions (ICH E2B format). Quantitative and qualitative analyses will be performed. The possibility of reporting of medication errors is already intensively promoted, e.g. at congresses or in journals.
Conclusion: The pilot project of DCGMA for recording and assessing of medication errors is an attempt aimed at improving patient safety. Existing structures need to be considered (e.g. coding) and adjusted if necessary (e.g. report form).
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P 080

Tacrolimus Side Effects in Tunisian kidney Transplant Recipients

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Background and objectives: Tarolimus, a calcineurin inhibitor, is an immunosuppressant used in renal transplantation to prevent rejection. It inhibits the mixed lymphocyte reaction and the formation of interleukin-2 by T lymphocytes. It is highly efficacious but it can induce toxicity. Correlation between high concentrations of tacrolimus and side effects was previously reported.
The aim of this study is to report side effects of tacrolimus in Tunisian renal transplant patients and to evaluate correlation between side effects and concentrations of tacrolimus.
Methods: It is a retrospective study (January 2010–April 2014) conducted in the department of Clinical Pharmacology in renal transplant recipients treated by tacrolimus. Therapeutic drug monitoring was carrying out by enzyme-linked immunoassay (ARCHITECT-ABBOTT). Abbreviated AUC0–12 h using three time points at T0h, T1h and T3h were measured.
Results: A total of 57 renal transplant patients were evaluated. 79 AUC0–12 h were collected. The median age was 30 years. The sex ratio (M/F) was 3.14. The average weight was 63.5kg. The mean dose was 0.11 mg/kg/day. The average AUC0–12 h in patients with side effects was 153.29 ng*h/mL versus 163.32 ng*h/mL in patients without side effects ($p = 0.87$).

Table 1 Side effects of tacrolimus

Side effects	Frequency (%)
Infections	35
Nephrotoxicity	24.56
Tremor	16
Hypertension	14
Diabetes	15
Dyslipidemia	3.57
Hyperkalemia	1.75
Diarrhea	1.75
Gingival hypertrophy	1.75

Conclusion: In our study such as in literature, infections and nephrotoxicity were the most frequent side effects. We did not found a significant difference between AUC0–12 h in patients with side effects compared to patients without side effects. Joy Varghese et al reported 21.9 % of neurotoxicity despite average trough concentration of 9 ng/mL and 28.1 % of nephrotoxicity despite average trough concentration of 6.7 ng/mL. So, side effects may be observed even with therapeutic tacrolimus concentration. This confirms that monitoring of patients receiving immunosuppressive drugs requires confrontation between clinical symptomatology and tacrolimus concentration.

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P 081

Gestational Pemphigoid Induced by the Anti-Tetanus Vaccine?

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Introduction: Vaccine is a powerful immune booster. This stimulation may cause an exacerbation of pre-existing autoimmune disease or induce autoimmune disorders in healthy patients.

Pemphigoid is an autoimmune disease. In literature, rare cases of pemphigoid have been induced by vaccination (1). We report a case of a pregnant patient at 18th week of gestation that developed gestational pemphigoid following injection of an anti-tetanus vaccine. This case was notified to the Centre National of Pharmacovigilance of Tunis on 23 October 2014 and analysed according the WHO method of imputability.

Case report: MA, is a 38 years-old pregnant woman, without any pathological history. Her first pregnancy was normal. On the 30th June 2014, at the 18th week of gestation, she received an injection of tetanus vaccine. One hour after, she started having itching at the injection site. The pruritus became generalized. Symptoms evolved to the appearance of some erythematous plaques initially. On the 14th August 2014, she developed some bullous elements on the hands and feet. Direct immunofluorescence showed the presence of a linear deposition at the dermal-epidermal junction of IgG and C3. The diagnosis of gestational pemphigoid was retained. Patient was treated with topical corticosteroids. Pregnancy was evacuated on 18 Aug 2014 since the patient developed preeclampsia. She was treated by oral corticosteroids. The eruption has regressed in a week.

Discussion and conclusion: The role of anti-tetanus vaccine was assessed as possible in front of a compatible delay (one hour after vaccination).

In literature, 27 cases pemphigoid eruptions were described after vaccination (1).

The influenza vaccine was most commonly associated with bullous pemphigoid (41 %) followed by the anti-tetanus vaccine combined with the diphtheria and pertussis (33 %). Only two cases have been reported after administration of anti-tetanus vaccine alone (1).

In literature, the period of occurrence of bullous pemphigoid after vaccinations varied from 5 hours to 5 weeks (1). For our patient, itching started one hour after vaccination, however the bullous eruption appeared six weeks after vaccination.

It remains difficult to distinguish between the normal outbreak of the autoimmune disease and the role of the vaccine in this outbreak since there has not been any antibodies tests before immunization (1).

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P 082

Acute Pancreatitis Induced by Metformin

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Introduction: The responsibility of drugs in the genesis of acute pancreatitis ranged from 0.3 % to 1.2 %. Metformin have been involved in rare cases, secondary to overdose or impaired renal function.

We report a case of acute pancreatitis in healthy patient without preexisting renal disease treated with metformin.

Case report: 73 old-years woman was treated with Amarel (glimeperide) from 6 years and Glucophage (metformin) from 3 years for diabetes type II. Her medical history was otherwise notable for hypertension from 20 years treated with Monotildiem® (diltiazem) and Physiotens® (moxonidine), coronary syndrome from 6 years treated with Pidogrel® (clopidogrel), Kardegic ® (lysine acetylsalicylate) and Torva® (atorvastatin).'

She had consulted on 11 May 2013, emergencies for epigastric pain and vomiting. The diagnosis of acute pancreatitis was suspected. The patient was hospitalized in the intensive care unit. On admission, physical examination was normal. Laboratory tests showed a hyperlipasaemia to 4000 IU/L, CRP to 300 mg/L and creatinine to 10 mg/mL. Abdominal ultrasound was normal, gallbladder was acalculous. Abdominal CT scan showed 3 casting necrosis which allowed classifying pancreatitis in Step E CT. The biliIRM showed no calculus.

She did not drink alcohol, no history of gallstones and no renal failure. Laboratory tests showed no hypercholesterolemia no hypertriglyceridemia no hypercalcemia.

Clinicians have stopped all treatments at the lack of other causes of acute pancreatitis.

After 3 days of symptomatic treatment, the patient improved. These clinicians passed to a semi-liquid diet and treated her diabetes with insulin. After 6 days, she took over all treatments except metformin and glimeperide. The outcome was favourable; there was no recurrence of the symptoms.

Two months after, glimeperide was reintroduced with no incident.

Discussion and conclusion: The role of metformin in the genesis of acute pancreatitis was strongly suspected with a score of Begaud to I2B3. In front of the delay of 3 years compatible with an iatrogenic origin, a favourable evolution after stopping this medication, the absence of other causes for the occurrence of this event, and the rechallenge of other drugs with no recurrence.

The exact mechanism of metformin induced pancreatitis is not known, but toxicity is probably secondary to acinar cell injury leading to intercellular leakage of digestive enzymes from ductules.

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P 083

Tolerability to Fixed-Dose Combination Antituberculosis Therapy

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Introduction/AIM: The fixed-dose combination antituberculosis therapy was introduced in the national program against tuberculosis in Tunisia since 2010. Few studies concerning the tolerability of this combination have been published.

We conducted a prospective study to identify the type, the frequency and the severity of side effects related to this association.

Methods: We include all patients who consulted in a medical dispensary for tuberculosis. We collected information concerning the concurrency of adverse effects following this association by regular monthly phone call.

Results: We collected 102 patients who were prescribed fixed-dose combination antituberculosis therapy. There were 55 men and 47 women. Sex ratio H/F was 1.17. Age varied from 8 to 84 years. Fifty nine patients presented 1 or more side effects. Side effects were variable. There were gastro-intestinal in 39.8 % including epigastralgia, nausea/vomiting, diarrhea and anorexia. Cutaneous side effects (26.3 %) were acne, rash, isolated pruritus and photoxicity. Asthenia represented 12.3 % of side effects. Neurosensoriel and neuropsychic side effects (9.9 %) were drowsiness, headache, decreased visual and auditive acuity, irritability and dysgueusia. Hepatic side effects (1.8 %) were relieved in 2 cases of hepatic cytolysis.

Among all side effects, 76 % occurred in the 1st month and regressed with maintaining the drug in 66 % cases of pruritus, 50 % cases of rash and in 49 % of gastro-intestinal manifestations.

In 3 cases/59, side effects required hospitalization.

Conclusion: Side effects of fixed-dose combination antituberculosis therapy were mostly mild. Gastro-intestinal and cutaneous adverse reaction were the most frequent ones. Some side effects were transient and didn't required drug withdrawal. Frequency and seriousness of adverse reactions in our study seems to be similar to those reported in the literature.

P 084

Bullous Eruption and Skin Necrosis Following Extravasation of Vinorelbine

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Introduction: Vinorelbine is a semi-synthetic vinka alkaloid used primarily in the treatment of advanced non-small cell lung carcinoma either alone or in combination with other chemotherapeutic agents. It is injected intravenously.

Skin necrosis from intravenous infiltration of soft tissue is a rare but serious complication of intravenous therapy. Vinorelbine was rarely associated with skin necrosis. We report a case of Skin necrosis following extravasation of vinorelbine.

Case report: A 53 years-old man was treated with several cycles of vinorelbine (25 mg the 1st and the 8th day) and cisplatine (80 mg the 8th day) after surgery for pulmonary cancer. On the 2nd day of the 3rd cycle, the patient complained about pruritic erythematous plaque on the left forearm around the site of injection. Three days later, the lesions presented with a central blister. Examination revealed an erosive area of 3 cm with an irregular shape surrounded by papules. The patient was treated by topic corticoid and local antiseptic. The course was favourable in 3 weeks. The next cycle, the injection site was moved to the right forearm. There were no further new skin lesions.

Conclusion: Vinca alkaloids are among the intravenous drugs with the highest destructive power [6]. Intravenous infusions of vinorelbine should be performed using the preventive measures and care applied for other chemotherapeutic agents with high potential for induction of skin necrosis due to extravasation. Mini-bags should be used for the administration of vinca alkaloids and this practice will prevent the inadvertent extravascular administration of vinca alkaloids via syringes.

P 085

Gender Differences in Pharmacokinetics of Tacrolimus

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Background and objectives: Tarolimus, a calcineurin inhibitor, is an immunosuppressant used in renal transplantation to prevent rejection. It is characterized by inter-and intra-individual pharmacokinetic variability and a narrow therapeutic range. Monitoring of tacrolimus using Area Under the Curve (AUC) is the best tool for dose adjustment.

There are biologic differences between men and women that can result in differences in responses to drugs.
The aim of this study is to evaluate the inter-patient pharmacokinetic variability of tacrolimus due to gender.
Methods: It is a retrospective study (January 2011–April 2014) conducted in the department of Clinical Pharmacology in renal transplant recipients treated by tacrolimus. Therapeutic drug monitoring was carrying out by enzyme-linked immunoassay (ARCHITECT-ABBOTT). Abbreviated AUC0–12 h using three time points at T0h, T1h and T3h were measured.
Results: A total of 37 renal transplant patients were evaluated. In our study, there were 24 men and 13 women (the sex ratio (M/F) was 1.84). 59 AUC0–12 h were collected (Table 1).

Table 1 Differences between genders

	Men	Women	p
Number of patients	24	13	–
Median age (years)	29.5	31	0.63
Average weight (kg)	71.5	55.5	0.39
Dose (mg/kg/d)	0.11 ± 0.05	0.129 ± 0.06	0.003
C0 (ng/mL)	7.25	8.26	0.82
AUC0–12 h (ng*h/mL)	165.35 ± 101.81	152.02 ± 90.66	0.052

Conclusion: Despite a higher dose of tacrolimus in women, AUC0–12 h was significantly lowest ($p = 0.052$). This is probably explained by a rapid metabolism of tacrolimus in women. Velicković-Radovanović R and al suggest that women have a higher activity of CYP3A4 than men (1). So, monitoring tacrolimus using abbreviated AUC seem the better indicator for evaluating exposition to tacrolimus.
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P 086

Safety of Brotizolam in Patients Hospitalized in Internal Medicine Departments

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Introduction: Sleep disturbance is common in hospitalized patients; the prevalence increases with age. Pharmacological treatment of this disorder consists mainly of hypnotic drugs that impose a risk of adverse reactions when taken by the elderly. The balance between the benefits of sleep improvement during hospitalization and the downside of the sleep medications is delicate. Brotizolam is a benzodiazepine medication used commonly for sleep induction; data regarding its safety in hospitalized patients is limited.
Aim: Evaluate the safety of brotizolam in hospitalized patients.
Methods: A single centre retrospective comparative analysis of a prospective cohort of patients hospitalized in internal medicine departments during 2012. Patients treated with brotizolam were compared to patients not treated with any benzodiazepines during hospitalization. Data were collected from medical records and subjected to rigorous statistical analysis. Primary outcome was any of the safety events: mechanical ventilation, delirium, and fall.
Results: 573 patients were randomly selected and studied; 297 treated with brotizolam (treatment) and 276 not treated with any benzodiazepines (control). Median ages were 82 and 75, in the treatment and control groups, respectively. Gender distribution was relatively equal; 52 and 54 % males, respectively. Morbidity burden of the patients evaluated by the Charlson score was not significantly different between groups. After adjustment, primary outcome occurred significantly higher in treated patients (18 vs. 2 events; adjusted RR = 3.6; CI95 % 1.3–9.6; $p = 0.012$). Any psychotropic medication during hospitalization was found by logistic regression as the main independent risk factor for the studied safety outcomes while age, comorbidities and the cause of hospitalization were not.
Conclusions: Treatment with brotizolam during hospitalization in internal medicine departments was linked to a higher risk of respiratory deterioration, delirium and falls. Psychotropic medications during hospitalization in internal medicine department are the main independent risk factor of safety outcomes in the studied cohort. Further research is needed to fully evaluate the risks and benefits of sleep induction medications in hospitals.

P 087

Educational Materials Can Have Positive Impact on Patients' Knowledge of ADRs—A Randomized Controlled Trial of Novel Educational Booklet

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Introduction: Patient reports of adverse drug reactions (ADRs) could contribute to the pharmacovigilance systems qualitatively as well as quantitatively. There are a lot of factors that influence patients' participation such as personal characteristics, disease perception, previous experience and education.
Aim: The aim of the study is to assess the role and potential of printed educational materials in improving patients' knowledge of ADRs.
Method: 40 patients (age 25–78) were randomized to receive either a two-phased patient-centred educational intervention (phase 1 included a15-min discussion with a pharmacist on adverse drug reactions and reporting; phase 2 included educational booklets intended to be reviewed by the patient later in their homes)—intervention group; or a one-phased intervention (15-min discussion with a pharmacist on adverse drug reactions and reporting)—control group. The primary outcome was patients' knowledge of ADRs assessed by check-list questionnaire filled in prior and after the intervention.
Results: 20 patients were randomized to receive a two-phased intervention and all of them completed the study. 20 patients were randomized in the one-phased intervention and 19 of them completed the study. By the study end the ratio of patients in the intervention group showed a statistically significant improvement in knowledge of ADRs than the patients in the control group. Patients in both groups shared experience of ADRs in the past that they have recognised after the intervention.

Conclusion: Distribution of educational materials can have positive effect on patients' knowledge of ADRs and facilitate their participation in the adverse drug reactions reporting systems.

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P 088

Adverse Drug Reactions Reporting By Patients—An Observational Study of the Bulgarian Pharmacovigilance Database

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Introduction: Direct patient reporting of adverse drug reactions (ADR) was introduced in Bulgaria in July 2012. There are no published local studies examining the quality and the content of patient reports.

Aim: The aim of the study is to analyse the adverse drug reactions reports after 3 years of experience and propose steps for improvement of direct patient reporting in Bulgaria.

Methods: In a retrospective case-series study, all cases of the adverse drug reactions (ADR) reported to the Bulgarian Pharmacovigilance Database between July 2012 and May 2015 were analysed. For each case the following data was recorded: age, sex, suspected drug, ADR description, concomitant disease/medication (if available). Causality link between the suspected drugs and the adverse drug reactions was performed using the WHO-UMC system for standardized case causality assessment.

Results: A total of 102 ADR cases were reported in 24children and 78 adults with 66 % occurring in females. The patients' median age was 34.2 (1–90) years. 60 % of the reported ADRs were classified as serious and46 % were classified as unexpected. According to the WHO-UMC system for standardized case causality assessment 55 % of the ADR were classified as possible and only 3 % as certain. ADRs from vaccines and other biotechnological products were most often reported.

Conclusion: Patients are willing to report ADRs the majority of which are classified as possibly related to the suspected drugs. Direct patient reporting could help to identify problems related to drug therapy and contribute to increased ADR reporting rates. Based on our previous studies and available data-base we could conclude that patients 'reports will be a valuable source for signal detection and improvement of pharmacovigilance system.

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P 089

Contraindications Involving Citalopram or Escitalopram in Clinical Practice: Relevance of the Pharmaceutical Analysis?

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Introduction: Citalopram and escitalopram are antidepressants SSRIs (selective inhibitor serotonin reuptake). Escitalopram is the therapeutically active (S)-enantiomer of citalopram. These drugs are widely used. As other psychotropic drugs, a dose dependent QT interval prolongation is described with these antidepressants. Several precautions including contraindications have been established to minimize the risk. One of the goal of Pharmacist Interventions (PI) is to prevent and monitor these contraindications, but, related to poor satisfactory therapeutic alternatives, PI are not always followed.

Aim: The objective of our work is to study the relevance of PI involving Citalopram or Escitalopram Absolute Contraindication (CEAC).

Methods: We studied all CEAC detected in a French polyvalent hospital of 600 acute beds during 6 months. The data were extracted from computerized prescriptions, involving 500 beds.We analyzed whether the PI was accepted or refused by physicians. In this practice, we followed two steps daily (1) Extraction of all CEAC detected by the software DXcare® which is interfaced with the Vidal database and (2) Analysis of all CEAC.The analysis included all medications associated with escitalopram and the following parameters were studied: dosage, contraindication, indications, interactions, availability and medications ie. level 1 of the french classification (Société Française de Pharmacie Clinique). If an Absolute Contraindication (AC) was detected, the pharmacist informed the prescribing doctor about the AC (phone or short computerized message in DXCare®) and the intervention follow-up evaluated.

Results: 57,857 prescriptions were analysed. We retrieved 2116 AC (637 patients) including 168 CEAC (50 patients). Those CEAC represented 50 medical prescriptions. Among CEAC, the different therapeutic classes coprescribed were cardiac drugs (52 %), psychotropic drugs (32 %), antibiotic (6 %) and others (10 %). Electrocardiogram (ECG) had been performed by physicians during patient hospitalization for 34 patients (68 %). Among the 50 PI mentioned during the study only 17 PI were accepted by the prescriber.

Conclusion: Despite pharmaceutical analysis, physicians may prescribe drugs with AC. In this study, the relevance of CEAC is challenged in the absence of electrocardiographic impact. Nevertheless, it would be interesting to monitor more systematically and longer these patients a. Moreover it is difficult to change to cardiac and psychotic medications, for patients hard to balance therapeutically. To our knowledge, no adverse effects related to these CEAC have been reported. An analysis of cases of adverse drug reaction related to CEAC had been performed from the pharmacovigilance centres, not showing a lot of cases declared (only three increases QT interval and two torsade de pointe).

P 090

Evaluation of a New Classification of Adverse Drugs Reactions (ADR): Applying DOTS to Spontaneous Reports

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Introduction: The classification of adverse drug reactions (ADR) described by Rawlins and Thompson, mainly based on pharmacological knowledge, is binary: type A dose dependant and predictable and type B not dose dependant and unpredictable. It remains the most widely used. However, in order to solve and improve the knowledge on ADRs, a new classification, the DoTS, with a three dimensional approach, (dose, time and susceptibility) has been proposed.
Aim: To compare the new classification to the previous using individual case reports of the French Pharmacovigilance Database
Methods: the two classifications have been retrospectively applied to all ADRs transmitted spontaneously from a University Hospital to the CRPV during one year. We restricted the analysis to the cases with only one suspected drug, regarding the complexity and the need for learning this new classification. Cases were anonymised and registered in a table with the following parameters: patient's characteristics including comorbidities, ADR description, seriousness and outcome, characteristics of the suspected drug (dose, indication, duration), and ADR's delay regarding drug use. For each parameter of the DoTS (Dose and Time relatedness and Susceptibility), a criteria was chosen within their subtypes. A junior pharmacist and a senior pharmacovigilant classified the cases and two senior pharmacovigilant made reconciliation.
Results: In 2013, from 1169 cases transmitted to the CRPV, 275 were from the University hospital and we selected 200 cases, 83 with one suspected drug and one reaction and 117 with one drug and several reactions. Using the Rowlins and Thompsons classification, we found 124 Type A (62 % of the total), 45 Type B (22.5 %) and 31 cases (15.5 %) non assignable.
For the DoTS classification, preliminary results show that the most frequent combinations were the association "hypersusceptibility/Rapid, First, Early", (53 cases 26.5 %), then "collateral early" (29 cases, 14.5 %) and "collateral, independent" (23 cases, 11.5 %). For 41 cases (20.5 %), dose and Time parameters were undefined. The most frequent susceptibility parameter was age (49 cases, 24.5 %), followed by disease (41 cases, 20.5 %).
Conclusion: This new ADR classification method is more detailed and considers the effect of dose, time of occurrence and risk factors of each patient. These parameters are interesting to assess the safety profile of a drug, but also to describe more accurately the safety profile of drugs use in a hospital to act on risk factors. However, its application requires good documentation and training.

P 091

Safety of Misoprostol for Labour Induction and Delivery, an Off-Label Use: Partnership Between Regional Pharmacovigilance Centres and Regional Health Agency

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Introduction: In July 2013, the federation of pharmacovigilance (PV) of Paris area, involving 6 regional centres, was officially created. Since September 2011, exchanges have been set up between the regional health agency, an administrative body in charge of ensuring the efficiency of the health care system and managing the risk and quality/safety of care for the entire region, and the federation, part of the national PV system. This collaboration aims at conducting Pharmacovigilance studies at a regional level, taking into account the local practices.
Misoprostol is a prostaglandin, approved world-wide as an anti-ulcer drug; but because of its uterotonic and cervical activity, it is widely off label used in obstetrics and gynaecology. Misoprostol seems to be effective for labour induction and delivery. Contrary to other prostaglandin preparations, it does not require refrigeration or parenteral administration and is cost effective, an important point in countries with budgetary constraints. But its use for delivery is controversial due to the lack of official approval of misoprostol for delivery.
Aim: evaluation of misoprostol use and safety for delivery, an off-label indication, at the regional level.
Methods: all maternity hospitals were identified. A specific questionnaire was sent to all obstetrical staffs and pharmacies of these hospitals.
Results:

- We identified a total of 95 maternity hospitals, for 11 million inhabitants. We had a final response of 82 (response rate of 86 %);
- Seven maternity hospitals use misoprostol for final delivery and 2 others have stopped this use but would like to restart it;
- The conditions of misoprostol utilization are similar: contraindication in case of scarred uterus, senior prescription, use after failure of dinoprostone;
- Only 2 hospitals have patient information consent;
- Related to the number of births for these maternity hospitals, the number of women treated with misoprostol for delivery was estimated around 3000/year;
- 16 cases of adverse drug reactions were transmitted to the federation between 1995 and 2014, 9 of them from a patient's organisation. Effects were, for foetus, foetal insult (8), encephalopathy or handicap (3), and for mothers, painful contractions (5), post-partum bleeding (4), uterine rupture (2). We observed a dissociation between patient's and medical report.

Conclusion: we demonstrated the feasibility of a regional enquiry for off label drug use. This first study suggests an acceptable level of risk. A clinical trial about misoprostol use for delivery is ongoing and the results will be available in the next few months.

P 092

Retrospective Study on Determinants of Ifosfamide Induced Neurotoxicity

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Introduction: Ifosfamide (IFO) is an alkylating agent used to treat a variety of malignancies. Central nervous system toxicity was one of the most frequently reported adverse reactions with IFO monotherapy: incidence estimated between 10-30 %. Some authors have suggested that a drug–drug interaction with aprepitant increased the risk of IFO neurotoxicity. Moreover, clusters of neurotoxicity cases associated with IFO generic formulation (EG) have been reported in France. Oncopediatricians of our hospital have observed a raise of ifosfamide-induced neurotoxicity cases.
Aim: To compare proportion of neurotoxicity cases before and after generic use or aprepitant use.
Methods: We conducted a retrospective descriptive study of IFO neurotoxicity cases. All patients treated with at least one IFO course between January, 2003 and October, 2014 were included. Data collected were demographic characteristics (age, gender), IFO indication, neurotoxicity signs, associated medications, administration of methylene blue and time of onset of neurotoxicity. Aprepitant is used, but not systematically, in the department since 2009 and generic formulation since January, 2013. To meet the aim, we conducted two comparisons of proportion of neurotoxicity cases corresponding to the periods before and after aprepitant use (2003–2008 versus 2009–2014) or generic use (2011–2012 versus 2013–2014).
Results: A total of 213 patients received IFO during the analysed period. Twenty-one patients presented an episode of neurotoxicity: 12 males and 9 females with median age of 13 years (1–20). The incidence is estimated at 9.86 %. The main indication was sarcoma ($n = 17$). Methylene blue has been used for 17 of them and the outcome was favourable for all patients. Neurotoxicity occurred after a median of 2 courses (1–10) with IFO brand-name and after 1 course with generic formulation. There is no significant difference between neurotoxicity frequency before and after aprepitant use ($p = 0.11$) or before and after generic use ($p = 1$).
Conclusion: Aprepitant and IFO are substrates of CYP3A4 and a pharmacokinetic interaction involving this metabolic pathway was suspected. Our study did not show significative difference between the periods before and after aprepitant use or generic use. However, our data indicate that neurotoxicity developed earlier in the generic group. Chenaf et al. observed the same result but reported a higher frequency with generic formulation versus brand-name of IFO. Further studies need to be performed to investigate this neurotoxicity, particularly since some clinicians reduced doses or stop IFO courses resulting in possible loss of therapy successful for the patients.

P 093

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Antiepileptic Drugs (AEDs): A Case-Non Case Approach from European Pharmacovigilance Database

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Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and potentially fatal cutaneous adverse drug reaction. The aetiology of DRESS is not well understood and different immune-mediated and/or drug metabolism-related factors have been postulated. Antiepileptic drugs with aromatic structure has been previously more frequently associated to DRESS than non-aromatic AEDs, for the potential to create epoxides.
Aim: To assess the reporting odds ratio (ROR) as measures for disproportionality of the association between AEDs and DRESS through the European pharmacovigilance database (EudraVigilance-EV).
Methods: A case/non-case analysis was performed by means of reporting odds ratios (ROR) from EV spontaneous reports (2005 to 2014) after elimination of duplications. MedDRA preferred term (PT): DRESS. Non-cases were patients with all other ADRs not treated with AEDs.
Results: The highest significant ROR was found for zonisamide (ROR: 15.70; 95 % CI 12.94^s19.06), phenytoin (ROR: 14.77; 95 % CI 13.45–16.23), phenobarbital (ROR: 13.89; 95 % CI 12.18–15.85), carbamazepine (ROR: 13.81; 95 % CI 13.10–14.55) and lamotrigine (ROR: 13.57; 95 % CI 12.59–14.63). A significant disproportionality has also been observed for levetiracetam (ROR 5.83; 95 % CI 5.09–6.67), clobazam (ROR: 5.74; 95 % CI 4.50–7.31), rufinamide (ROR: 5.66; 95 % CI 2.11–15.18), perampanel (ROR: 5.55; 95 % CI 1.38–22.30), valproate (ROR: 4.56; 95 % CI 4.14–5.03), ethosuximide (ROR: 4.75; 95 % CI 1.96–11.47), eslicarbazepine (ROR: 4.30; 95 % CI 1.07–17.25) and oxcarbazepine (ROR: 3.60; 95 % CI 2.86–4.54). Lacosamide (ROR: 2.66; 95 % CI 1.42–4.95), primidone (ROR: 2.35; 95 % CI 1.05–5.25), topiramate (ROR: 1.65; 95 % CI 1.20–2.27) and gabapentin (ROR: 1.40; 95 % CI 1.10–1.76) was associated with the lower values. No significant ROR and/or no reports are available for other AEDs.
Conclusion: According to our results, the presence of an aromatic ring in the chemical structures of AEDs may partly explain the association with DRESS. Contrary to what expected some new AEDs with aromatic structure and different metabolic pathway showed a lower disproportionality ratio than classical aromatic AEDs.

P 094

Potential and Actual Drug–Drug Interactions in Elderly Patients Admitted to an Emergency Department: Data from the ANCESTRAL-ED Study

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Introduction: Drug–drug interactions (DDIs) in elderly patients can induce severe adverse drug reactions (ADRs) leading to admission to emergency department (ED). This study was performed to determine the frequency and characteristics of potential DDIs among elderly patients presenting at ED, and to assess which potential DDIs can result in clinical signs and symptoms consistent with the reason for ED admission.
Methods: The present analysis evaluated data collected during the ANCESTRAL-ED study. This retrospective study is based on the evaluation of ADRs, DDIs and appropriate drug prescription in elderly patients (≥65 years) admitted to the ED of Pisa University Hospital (Italy) between May 2012 and May 2014. "Potential" DDIs were assessed using Thomson Micromedex®, and classified on the basis of their clinical relevance (contraindicated, major, moderate, minor). Each ED admission (discharge diagnosis) consistent with the signs and symptoms expected for a potential DDI was classified as an "actual" DDI.
Results: Throughout the study period, 3,005 ED admissions (1899 patients, 58 % females, mean age: 80.3 years) were recorded. An overall number of 16,662 drugs were evaluated and the mean number of drugs for patient was 5.1 ± 3.4. Acetylsalicylic acid (ASA), furosemide and pantoprazole were the most frequently used medications. The overall number of potential DDIs was 7451 (41 contraindicated; 2000 major; 5208 moderate; 197 minor and 5 not defined), and were detected in 1899 (63 %) patients. The drug combination expected to result in the most frequently recorded DDI was ASA plus furosemide (decreased diuretic and antihypertensive efficacy of furosemide), reported in 324 cases (4 %). Overall, 301 DDIs were found to be consistent with ED admission in 194 patients (representing 10.22 % of patients with potential DDIs and 6.46 % of the overall number of patients included in the cohort). Allopurinol in combination with warfarin (bleeding) was the most frequently reported actual DDI (6 cases), followed by levothyroxine + warfarin (bleeding, 5 cases), ASA + amlodipine (gastrointestinal hemorrhage and/or antagonism of hypotensive effect, 5 cases) and ASA + furosemide (5 cases).
Conclusion: More than half of elderly patients admitted to ED presented at least a potential DDI among drugs taken at the time of admission. Notably, only 4 % of potential DDIs accounted for an event actually related to ED admission. Educational efforts and consequent awareness of prescribers about the risk of potential DDIs in the elderly would help to prevent actual DDIs and improve patient care. A close monitoring of ADRs due to DDIs should be implemented by large observational studies.

P 095

QT Interval Prolongation and Hydroxyzine: A Retrospective Cohort Analysis on Hospitalized Elderly Patients

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Introduction: The European Medicines Agency has issued a warning concerning a potential association of hydroxyzine, an antihistaminic, employed off-label as sedative in the elderly, with long QT syndrome.
Objective: The present analysis evaluated the effect of hydroxyzine on corrected QT (QTc) interval in hospitalized elderly patients.
Methods: This retrospective cohort analysis was conducted on patients ≥65 years-old, enrolled between July 2012 and July 2014 in the ANCESTRAL program, an observational study aimed at detecting adverse drug reactions in elderly patients admitted to Emergency Department (ED) and hospitalized in the geriatric ward. The ANCESTRAL database contains demographic data and clinical information assessed at ED admission. Patients were included if their records reported a complete medical history for at least 3 months prior cohort entry. The patients entered the cohort if hospitalization was required after the ED visit. During the first week of hospitalization, each patient underwent routine ECG. After cohort entry, each patient was followed up until the first ECG, discharge or death. Main outcome was defined by abnormal QTc (>451 ms for males, and >471 ms for females). Current exposure was defined at cohort entry by at least one record for hydroxyzine use in the 3 months preceding hospitalization. Relative risk (RR) for abnormal QTc was estimated by Poisson regression and adjusted for the following covariates assessed at baseline: age; gender; exposure to drugs known to affect the QTc interval; heart diseases; electrolyte abnormalities.
Results: The final cohort included 182 patients. No patient died or was discharged before an ECG was performed. 34 patients (41 % females, mean age: 86.26 ± 8.53) were classified as exposed to hydroxyzine [dose: 12.5 mg/day (n = 13) and 25 mg/day (n = 21)] and 148 (61 % females, mean age: 79.36 ± 7.49) not exposed. In patients exposed and not exposed to hydroxyzine, QTc ranged from 401 to 492 ms (mean QTc: 442 ms) and from 334 to 500 ms (mean QTc: 410 ms), respectively. The proportion of patients with abnormal QTc were 29 % (n = 10) in the hydroxyzine group and 10 % (n = 15) in the control group (RR:2.90; 95 % CI 1.30 to 6.45; p = 0.014). After adjusting for covariates, the RR resulted not significant (RR:1.87; 95 % CI 0.77 to 4.58; p = 0.16).
Conclusions: According to our analysis, current exposure to hydroxyzine up to the dose of 25 mg/day is not associated with a significant increment of QTc interval, as compared to not-exposed patients. Further studies with a larger sample of patients are required to confirm this finding.

P 096

From risk assessment to the risk management in the use of radiological iodinated contrast media (RICM)

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Introduction: Radiological Iodinated Contrast Media (RICM) are substances that potentially can generate adverse reactions (ADRs), even

deadly ones, with a reported frequency from 5-8 % that is directly related to its osmolality. Unfortunately, in many cases their use cańt be replaced, because they represent a useful tool for early diagnosis, being essential in every case, to assess the benefit–risk ratio that its use implies.

Aim: To Identify, quantify and evaluate the risk caused by to the administration of contrast media in patients undergoing radiologic studies in order to propose a Risk Management Plan for the Hospital Universitario de Puebla (HUP), based on the real nature of our population, so as to provide a greater safety for patients.

Methodology: An active pharmacovigilance study was conducted in patients undergoing ICM in the Department of Radiology and Imaging (DRI) of the HUP, from February to June, 2014, in order to assess the risk, according to the NOM-220-SSA1-2012 Installation and operation of Pharmacovigilance.

Results of the risk analysis were provided to the Head of DRI and to the Pharmacy and Therapeutics Committee (PTC) that is responsible for Drug Utilization Policy at the HUP.

Results: During study, 457 computerized topographies (CT) were performed at outpatient and inpatient; 155 (34 %) patients were under the effect RICM. 16 patients (10.3 %) expressed at least one ADR, being the main symptoms: feeling of hot, nausea, pruritus, dysgeusia and dizziness. Two patients, due to the intensity of the reaction (severe) required care in the emergency room and in 50 %, possible interactions with concomitant pharmacotherapy were identified.

After communication of results to the DRI medical staff, a Risk Management Plan was proposed to the PTC, including: 1. to develop a Standard Operating Procedure for the management and use of the ICM, which includes a bitacore where the acquisition, identification, verification and validation are recorded. 2. Reactivation of the "Protocol for the Evaluation of Risk Factors for RICM", (previously submitted by the CIFV BUAP-FCQ) and, 3. To spread the decisions taken by the PTC to all health staff at HUP.

Conclusions: The risk of ADR due to the ICM administration at HUP population (10.3 %) is higher than reported internationally. It is necessary to carry out studies and intensive pharmacovigilance, in order to identify risks that provide warning signals and further establish a Risk Management Plan that favours a Rational and safe Use of Medicines.

P 097

Adverse Drug Events Related To Approved Prophylactic Use of Omeprazole

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Introduction: The method of spontaneous reporting is characterized by limitations of underreporting and low data quality. In this context, methodologies are necessary that promote the effectiveness and safety of omeprazole, which is widely use, most notably for prophylaxis. However, omeprazole is associated with several adverse drug events (ADE) [1, 2] due to its abuse or unreasonable prescription. This situation may result in the ineffectiveness of the medicine and a decrease in patient safety.

Objective: The study aimed to identify and assess the risk of ADE and the benefits of effective prophylactic use of omeprazole in hospitalized patients.

Methods: We conducted an observational cohort study from August until October 2013 and December 2013 until May 2014 in the Américo Brasiliense State Hospital in São Paulo, Brazil. The inpatients were placed into three groups: (a) patients using prophylactic omeprazole in an approved way, (b) patients using prophylactic omeprazole in an unapproved way and (c) patients not using omeprazole. The patients who did not use prophylactic omeprazole were excluded. The patients were monitored daily with the aid of appropriate research guide previously. The data were tabulated according to the presence or absence of effectiveness and ADE in the three groups.

Results: We focused on 427 hospitalized patients, of which 136 hospitalized patients received unapproved prophylactic omeprazole and 52 received approved prophylactic omeprazole. We observed two cases of suspected ineffectiveness and 14 ADE. There was a significant difference in serum creatinine and urea in patients using approved prophylactic omeprazole regarding control group and unapproved use.

Conclusion: There was no association of prophylactic omeprazole with risk factor; however, there was a significant difference in the increase in serum creatinine and urea in patients receiving approved prophylactic omeprazole. These data highlight the need for further prospective studies to evaluate the chronic use of omeprazole and renal functioning.

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P 098

Patient Reporting Systems: A View Across the European Union

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Introduction: New Pharmacovigilance legislation (Directive 2010/84/EU) allows patients to report adverse drug reactions (ADRs) directly to competent authorities in all European Union (EU) member states. The impact of direct patient reporting in some countries is already very positive in order to facilitate a better understanding of consumer perspectives. The quality of patient reports is similar to that of health professionals, providing also useful information about the impact of ADR in their life.

Aim: To characterize the ADR' reporting systems for patients trough EU and describe the changes occurred due to new pharmacovigilance legislation and the evolution of in ADR' reporting systems.

Methods: A review was performed looking for the changes in reporting systems across EU, before and after implementation of new pharmacovigilance legislation. The analysis was based in bibliographic review and annual reports of different countries. Several variables were analysed: total number of reports per million inhabitants, percentage of reports made by patients, means of reporting, feedback given to patients.

Results: Spontaneous patient reporting systems of 28 countries were evaluated. Direct reporting of suspected ADRs by patients have been initiated few years ago in Europe, and pilot systems were launched firstly in The Netherlands (2003), Denmark (2003) and the UK (2005) and more recently in other countries; however, some countries does not reject

reports from consumers before, even without having an official implemented system for that purpose. Countries with older systems, such as Netherlands, Denmark and Sweden, have about 21–35 % of reports were collected directly from patients; On the other hand in some countries the value is residual.
Conclusion: Patient' reports became accepted mandatorily by all countries through European Union, although, their contribution to Pharmacovigilance is quite variable. The older systems and those who promote the system have better results in reporting levels. The contribution of patients for pharmacovigilance is often considered important and useful in terms of information given and quality of reports, contributing to a better knowledge and improvement of medicines.

P 099

Mitoxantrone Treatment-Induced Cardiotoxicity in Patients with Multiple Sclerosis

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Introduction: Multiple Sclerosis (MS) is a chronic, autoimmune, neurodegenerative and demyelinating disease of the central nervous system, which affects the quality of life of patients and their families. This disease is characterized by relapses or exacerbations, which are clinical consequences of increased inflammatory activity in the CNS. Few treatment options for patients with secondary progressive multiple sclerosis (SPMS) is available. Mitoxantrone (type II topoisomerase inhibitor) could be used to treat MS, most notably the subset known as SPMS. Mitoxantrone will not cure MS, but could be effective in slowing the progression of SPMS and extending the time between relapses in relapsing-remitting MS and progressive relapsing MS.
Aim: Systematic assessment of the scientific evidence on the efficacy and safety of Mitoxantrone use in patients suffering from MS.
Methods: A systematic critical review without meta-analysis was conducted through information collection in electronic databases such as PubMed, B-On, ScienceDirect, Elsevier and SciELO. Language restriction to Portuguese, Spanish and English was applied. PICO parameters were applied and the following keywords were used: Cardiotoxicity, Mitoxantrone, Multiple sclerosis and Safety. Were selected items with less than 10 years from 2005–2014, full access and interest. The final selection of relevant items was done by full reading and giving priority to original articles.
Results: Conventional therapy includes immunomodulatory and immunosuppressive drugs, which act at different stages of the disease and reduce the frequency of relapses or exacerbations, control the symptoms exacerbation and delay long-term disability. The available therapy isn't completely safe, due to its adverse effects, however, there are patients who have an effective response. Many drugs have been investigated to provide a better quality of life to the patient. Mitoxantrone is an anthracenedione synthetic agent originally developed for cancer treatment. Preclinical studies have also shown that mitoxantrone has immunosuppressive properties, leading to clinical investigation in patients with MS. Currently this drug is approved in the USA and Europe for the treatment of the most active MS forms. The use of mitoxantrone, in patients with MS, is associated with significant risks, such as cardiotoxicity.
Conclusion: The use of mitoxantrone should be carefully considered, and doctors should prescribe the smallest possible cumulative dose to reach clinical effects and desired monitor patients during and after the treatment. Effectively each administration of mitoxantrone should be accompanied by monitoring cardiac function to improve the safety of treatment for patients and enable early detection of any side effects, especially in high risk groups.

P 100

Compromise of the Effectivity of Oral Contraceptives in Concomitant Use with Antibiotics

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Introduction Oral hormonal contraception is the most widely used method worldwide for women in preventing unwanted pregnancy by removing the follicular stimulating hormone (FSH) in the ovarian cycle. The concomitant use to other drugs could induce hormone blockade. Among the described medicines, the possible interactions between oral antibiotics and oral contraceptives (OC) remain a subject that generates controversy among the scientific community. Co-administration with potent enzyme inducers of microsomal hepatic metabolism, as rifampicin, can increase the hepatic catabolism of estrogen or progestogen, reducing the half-life and respective effectivity.
Aim: To assess the interaction between OC and antibiotics and characterize the mechanisms involved in the effect of the antibiotic therapy with OC's.
Methods: A systematic review was conducted from the PubMed, Medscape, SciELO. Language restrictions to Portuguese, Spanish and English were applied. PICO parameters were applied and the following keywords were used: (patients OR individuals OR person OR women) AND (antibiotics) AND (oral contraceptives) AND (drug interaction) AND (efficacy) AND (pregnancy). Articles were selected based on information related to antibiotic therapy and OC's efficacy relationship. A total of 30 articles were selected for analysis.
Results: In 1974, Reimers reported that five of 88 women who used CO and rifampicin were pregnant. Swenson (1980) found an increased excretion and reduced half-life plasma of ethinylestradiol in 5 women taking OC, and 4 were treated with tetracycline and ampicillin Moreover, Back et al. (1990) observed 13 oral contraceptive users women who were also taking ampicillin and not found hormonal changes in plasma concentrations compared with previously controlled cycles. The explanation for these conflicting results may be related to individual variations in the metabolism of OC. The women may have low bioavailability of ethinylestradiol due to the extensive metabolism of steroids in the intestinal wall and liver, large intrahepatic circulation of ethinylestradiol and intestinal flora particularly susceptible to antibiotics.
Conclusion: Rifampicin is the only antibiotic scientifically proven interaction, to accelerate metabolism of OC, through the induction of CYP450, leading to decreased effectivity. Most of the analyzed antibiotics decreased the level or effect of OC indirectly by altering intestinal flora, remaining a low risk of contraceptive failure. However, the main adverse reactions reported with the use of antibiotics include: nausea, vomiting and diarrhoea, which could also have interference on the efficacy of OC's. Information to women is essential to manage this interaction and to ensure the oral contraceptive effectivity.

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Right-Sized Signal Detection Systems that Meet Regulatory Expectations

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Introduction: The requirement to properly plan, track and manage signals from all sources has never been greater. Over half the signals managed by the European Medicine Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) in its first year of operation, resulted in changes to the product information* and we are seeing an increasing focus by inspectors on signalling strategies. We describe approaches to fit-for-purpose signal detection and management strategies in different-sized biopharmaceutical companies.

Overview: Whether a company holds one or multiple product authorizations, a robust, cost-effective, compliant signal detection and management system is central to any PV program. Regulatory expectations are increasing and a quality framework must be demonstrated by all stakeholders. We presents case studies of the use of tailor-made signalling strategies in small to large-sized pharmaceutical company, with a focus on quality management.

Abstract Details: Regulatory expectations for proper signal management, including appropriate signal detection strategies, are more stringent than ever. In the EU, transparency, compliance and quality are critical elements of the pharmacovigilance legislation. Regulators and PRAC are making increased use of EudraVigilance with detected signals currently published each month and available to the EU Qualified Person for Pharmacovigilance (QPPV) and general public. FDA continues to expect strong and swift signal detection and analysis throughout a product's lifecycle. We will present the correct application of the signal management process including the importance of terminology, strategy setting, tracking, timely decision making and escalation processes.

We will also present the current signal detection and management regulatory landscape in a number of major jurisdictions before moving on to practical examples of signalling strategies in different types of companies.

**Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8–11 September 2014, accessed 12 Sep 2014*

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The Effect Of Curcumin On Experimental Non-Alcoholic Fatty Liver Disease in Rat Models: Biochemical, Histochemical and Immunohistochemical Studies

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Introduction: Non-alcoholic fatty liver disease is the most common and emerging form of chronic liver disease worldwide. [1] Nuclear factor-kappaB is a nuclear transcription factor closely related with inflammation. [2] Curcumin, extracted from the rhizome of herb Curcuma longa, is widely reported to have potent anti-oxidative, anti-inflammatory and anti-carcinogenic effects.

Aim: To investigate the effect of curcumin on experimental non-alcoholic fatty liver disease biochemically, histochemistry and immunohistochemistry.

Methods: Wistar male rats were divided equally into four groups**: G I**: Control group **GII**: Fatty liver group, **GIII**: Fatty liver group injected intraperitoneal with 1 ml/kg body weight dimethyl sulfoxide (DMSO) and **G IV**: Fatty liver group injected intraperitoneally with curcumin dissolved in DMSO at dose of 50 mg/kg body weight. The investigations were done on serum, liver sections and homogenate.

Results: Serum ALT and AST and alakalinephosphatase activities were significantly lower in curcumin group compared to NAFL group. Serum insulin, glucose, triacyglycerides and HOMA-IR were significantly lower in curcumin group when compared to NAFL group. Triglycerides concentrations in liver extract of curcumin group were significantly lower than that of NAFL group. Serum LDL-cholesterol and VLDL concentrations were significantly lower in curcumin group when compared to NAFL group and DMSO group. MDA concentrations in liver homogenate were significantly decreased whereas total glutathione levels were significantly increased in curcumin group compared to NAFL group. Histopathological results of NAFL group revealed evidence of marked hepatic degeneration with the presence of micro and macrovesicular steatosis while curcumin treatment showed more or less the appearance of normal structure. Catalase activity was decreased after NAFL induction and increased after treatment by curcumin. Curcumin treatment in group IV significantly decreased activity of NF-kB when compared to NAFL and DMSO groups

Conclusion: Curcumin has reduced the markers of oxidative stress and inflammation in the liver, inhibited NF-kB expression, and improved the serum lipid profile. Therefore, curcumin has a favourable effect in NAFL.

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Number Needed to Harm as a Tool for Post-Marketing Drug Safety Evaluation: a Pilot Study with Thiazolidinediones

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Introduction: The benefit–risk ratio of rosiglitazone, a thiazolidinedione used in the treatment of diabetes mellitus (DM) type 2, was re-evaluated by regulatory authorities (RAs) due to a suspicion of an increased cardiovascular (CV) risk [1, 2]. While the EMA decided to withdraw rosiglitazone from the market, the U.S. FDA allowed the drug to continue

being marketed [3, 4]. There is a rational to study safety assessment processes of marketed drugs in the context of benefit–risk re-evaluations.
Aim: To investigate the usefulness of metric indices in post-marketing safety evaluations by estimating number needed to harm (NNH) values for CV adverse outcomes for rosiglitazone and pioglitazone.
Methods: Reports from RAs were consulted and a Medline search was performed to identify studies assessing CV risks [all-cause death, CV-death, myocardial infarction (MI), stroke or congestive heart failure (CHF)] for thiazolidinediones. Meta-analyses were performed to determine pooled evidence from randomized controlled trials (RCTs) and observational studies (OS). NNHs [with 95 % Confidence Intervals (CI)] per year were estimated for CV adverse outcomes.
Results: Reports from RAs included two meta-analyses of short-term RCTs, two long-term RCTs (RECORD and PROACTIVE), and a systematic review of OS (n = 29). The Medline search identified six additional OS. Statistically significant NNH values were obtained for (1) rosiglitazone vs. control on MI and CHF in the meta-analysis of RCTs (NNH = 16; 95 % CI = 10-255; and NNH = 7; 95 % CI = 5–16;respectively) and meta-analysis of OS (NNH = 12; 95 % CI = 9–20; NNH = 5; 95 % CI = 32–131;respectively), and on CHF in the RECORD (NNH = 6; 95 % CI = 4–14); (2) pioglitazone vs. control on CHF (NNH = 11; 95 % CI = 6, 403) in the meta-analysis of RCTs and PROACTIVE (NNH = 12;95 % CI = 8–43); (3) rosiglitazone vs. pioglitazone on MI (NNH = 69; 95 % CI = 32–379), stroke (NNH = 36; 95 % CI = 20–225), CHF (NNH = 33; 95 % CI = 19–47) and all-cause death (NNH = 63; 95 % CI = 49–100) in the meta-analysis of OS.
Conclusion: The NNH values suggest an increased CV risk with rosiglitazone versus pioglitazone across several sources of information. The inclusion of metric indices in the evaluation process can contribute to improve benefit–risk assessments of marketed drugs and, consequently, lead to better regulatory decisions on drug safety.
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Antibiotics-Induced Liver Injury: A Pharmacovigilance Study Using a Measure of Disproportionality in a Database of Spontaneously Reported Adverse Events

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Introduction and aim: Antibiotics are considered as a common cause of hepatotoxicity. The aim of this study was to identify the disproportionalities of associations between hepatobiliary adverse events and antibiotics in the Portuguese Pharmacovigilance Spontaneous Reporting Database.
Methods: Adverse events spontaneously reported to the Portuguese Pharmacovigilance System (PPS) between 2009-01-01 and 2013-12-31 were included. Adverse events were classified according to MedDRA (17.1) in the Preferred Term (PT) and primary System Organ Class (SOC). The Reporting Odds Ratio (ROR) and its 95 % Confidence Intervals (CI) were calculated for drugs classified in the Anatomical Therapeutic Chemical (ATC) class "Antibacterials for systemic use" regarding adverse events included in the SOC "Hepatobiliary disorders". Calculations were performed only for combinations involving a drug and at least four reports of an adverse event. Microsoft Excel was used to perform all the calculations.
Results: The PPS received 12,592 spontaneous reports of adverse events. "Antibacterials for systemic use" were suspected drugs in 1064 (8 %) cases. Of the 109 adverse events classified in the SOC "Hepatobiliary disorders", 21 (19 %) were reported in association with "Antibacterials for systemic use". Levofloxacin and meropenem (each, n = 5; 24 %) were the most common drugs. The most frequently reported events were "hepatitis toxic" (n = 8), "hepatotoxicity" (n = 3), and "hepatitis acute" (n = 3). Statistically significant RORs were found for "Antibacterials for systemic use" and "Hepatobiliary disorders" (ROR: 2.62; 95 % CI: 1.62–4.23), particularly "hepatitis toxic" (ROR: 7.93; 95 % CI: 3.18–19.76). Individually, levofloxacin and meropenem were associated with a statistically significant ROR for "Hepatobiliary disorders" (ROR: 11.07; 95 % CI: 4.34–28.22, and ROR: 37.46; 95 % CI: 13.47–104.15, respectively). Meropenem was also associated with "Hepatitis toxic" (ROR: 196.96; 95 % CI: 59.25–654.68).
Conclusion: Compared to all other drugs, antibiotics, particularly levofloxacin and meropenem, were disproportionately associated with hepatobiliary adverse events. Physicians and regulatory authorities should be aware of serious liver injury induced by these drugs and be able to identify and minimize its risk.

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Ocular Adverse Drug Events: Analysis of Spontaneous Reports from a Portuguese Regional Pharmacovigilance Database

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Introduction: Ocular disorders may be induced not only by drugs administered directly into the eye, but also by systemically administered drugs, which reach the eye through the vascular supply. The association between ocular adverse events (AE) and the use of systemic drugs was addressed in recent studies based on post-marketing safety data [1, 2].
Aim: The aim of this study was to evaluate ocular AEs associated with the use of drugs by analysing the content of the spontaneous reports received by the Central Portugal Regional Pharmacovigilance Unit.

Methods: The spontaneous reports received by the Central Portugal Regional Pharmacovigilance Unit between January 2001 and March 2015 were considered. The AEs were assessed according to their seriousness, previous knowledge and causal relation with suspected drugs. The ocular AEs were codded in the preferred term (PT), according to the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0. The suspected drugs were coded according to the second-level therapeutic subgroup of the Anatomical Therapeutic Chemical (ATC) classification system.

Results: The Pharmacovigilance Unit received 114 cases that contained 136 ocular AEs. Seventy cases (62 %) were assessed as serious, 40 (35 %) as unknown (i.e., not listed in the Summary of Product Characteristics [SmPC] of the suspected drug), and 69 (61 %) as being at least possibly related with the suspected drug. The most frequently reported ocular AEs were "visual impairment" (n = 26; 19 %), "periorbital oedema" (n = 21; 15 %), "eyelid oedema" (n = 13; 10 %), and "vision blurred" (n = 11; 8 %). "Antiinflammatory and antirheumatic products" (n = 20; 18 %), followed by "Antibacterials for systemic use" (n = 14; 12 %), and Ophthalmologicals" (n = 10; 9 %) were the suspected drugs most frequently reported.

Conclusion: Approximately one-third of the ocular AEs were not listed in the SmPCs of the suspected drugs, supporting the importance of spontaneous reporting to identify new safety signals. Further, the majority of the ocular AEs were reported in association with systemic drugs. In the light of such findings, healthcare professionals need to be aware of drug-induced AEs in the eye to avoid their progression, as they can lead to visual impairment.

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Henoch-Schönlein Purpura and Drug and Vaccine Use in Childhood: A Case–Control Study

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Background: Henoch-Schönlein purpura (HSP) is the most common vasculitis in childhood, nevertheless its etiology and pathogenesis remain unknown despite the fact that a variety of factors, mainly infectious agents, drugs and vaccines have been suggested as triggers for the disease. HSP following drug and vaccine administration has been described in case reports and in observational studies conducted during vaccination campaigns.

Aim: To estimate the association of HSP with drug and vaccine administration in a pediatric population.

Methods: An active surveillance on drug and vaccine safety in children is ongoing in 11 clinical centres in Italy. Are enrolled in the study all children (age >1 month and ≤18 years) hospitalized through the Emergency Departments (ED) for specific acute conditions. During children hospital admission, a trained pharmacist/physician interviewed parents to collect demographic and clinical information. Data on drug exposure in a time window of 3 weeks preceding hospitalization, extended to 12 weeks for vaccines, were collected. For all children the inclusion in the study was based on the diagnosis retrieved from the ED clinical record independently from drug and vaccine exposure. A case-control study design was applied for risk estimates: exposure in children with HSP, included as cases, was compared with similar exposure in children with gastroduodenal lesions, enrolled as controls. HSP cases were validated according to EULAR/PRINTO/PRES criteria. Validation was conducted retrieving data from individual patient clinical record.

Results: During the study period (November 1999–April 2013), 288 cases and 617 controls were included. For the validation phase of HSP cases, clinical records of 298 children (81 % of total), were retrieved. Only 10 cases did not fulfil the diagnostic criteria for the disease according to EULAR/PRINTO/PRES criteria. In all the remaining 288 HSP validated cases, a palpable purpura was present, accompanied by arthralgia/arthritis in 85 %; abdominal involvement, abdominal pain, melena, intussusception, in 65 %; renal involvement, hematuria, proteinuria, in 35 % and scrotal swelling in 7 %. In the same period 617 children were enrolled with gastroduodenal lesions. No significant increased risk was estimated for any drug. The risk estimated for HSP within 12 weeks after vaccination resulted higher, more than 3 times, for MMR vaccines with an OR of 3.3 (95 % CI 1.1–9.8) while no increase in risk was observed for any vaccine.

Conclusions: This study provides further evidence on the role of MMR vaccine in HSP occurrence.

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Liver Toxicity During Methotrexate Treatment: Analysis of Spontaneously Reported Cases in Serbia

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Introduction: The efficacy and tolerability profile of methotrexate (MTX) in the treatment of rheumatoid arthritis (RA) is well established, but liver toxicity associated with chronic low-dose MTX has always remained a concern [1–3].

Aim: The purpose of this work was to determine risk factors for MTX-induced liver injury in patients with RA and to analyze the demographics and clinical characteristics of these patients.

Methods: All cases of MTX-associated liver damage in patients with RA spontaneously reported to the National Pharmacovigilance Centre (during the period 2010-2014) were analyzed, and liver damage type and severity

were evaluated. A transaminase level of three times the upper limit of normal (ULN) on two or more occasions was taken to indicate hepatic injury. Transient serum enzyme increases were considered serious if they were ≥ 3-fold that of ULN and accompanied by increases in total bilirubin and INR or clinical symptoms of hepatic illness (anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine or jaundice).

Results: A total of 54 cases of MTX-induced hepatic abnormalities were studied. Mean age of these patients was 56.3 years, with female gender predominance (60.6 %). Out of the 54 cases, 19 cases (35.2 %) were serious (hospitalization were required in 5 cases and medical intervention in 8 cases, while permanent discontinuation of MTX in all serious cases). In 19 serious cases, the predominating type of liver damage was cholestatic hepatitis (13 cases), while hypersensitivity features (thrombocytopenia) were manifested in 6 patient. Concomitant medications were reported in 5 serious cases (systemic antimycotics, nonsteroidal anti-inflammatory drugs, proton-pump inhibitors, statins etc.). In the observed 5-year period, MTX-induced hepatic abnormalities presented 40.9 % of all reported hepatotoxicity cases and MTX was the leading cause of toxic liver injury. Concomitant use of hepatotoxic drugs, presence of comorbid conditions (e.g. diabetes, hypertension, obesity), lack of folic acid supplementation and abnormal baseline level of aminotransferases (AST and ALT), were risk factors for MTX-induced hepatotoxicity.

Conclusion: MTX-induced hepatotoxicity is a major problem in Serbian patients with RA and cause treatment interruption in 35.2 % of patients.

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Potential Drug–Drug Interactions in Patients Admitted to the Cardiology Ward of a Romanian Teaching Hospital

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Introduction: Patients with cardiovascular disorders are at high risk for drug–drug interactions because of the increased number of drugs prescribed concomitantly. Drug–drug interactions (DDIs) are an important cause of drug-related-problems detected in hospitals and may have an important impact on morbidity, mortality and health-care costs. Although DDIs are reported to be common, data regarding the prevalence and types of potential DDIs among patients admitted to the cardiology ward in Romania is still sparse.

Aim: To characterize the types of potential DDIs detected in a cardiology ward and to identify their pattern, while correlating them with laboratory tests' results.

Methods: A series of cases from the cardiology ward of the Cluj-Napoca County Hospital were assessed for the presence of potential DDIs. Micromedex© Solutions and PubMed were accessed for support. For each case where at least one DDI was identified, laboratory tests' results were used to check for actual interactions.

Results: Eighty-five cases were assessed, resulting in the identification of 23 pDDIs, involving 21 cases (median age 66.1 years), thus presenting an incidence of 24.7 %. Most common pDDIs were those between aspirin and acenocoumarole, digoxin and simvastatin, and acenocoumarole and simvastatin. Drug classes most commonly involved were antiplatelets, anticoagulants and statins. The majority of DDIs were of moderate severity. Some of the potential DDIs detected manifested and were documented.

Conclusions: The present study detected pDDIs and documented actual DDIs. The results of the study underline the need for prescription checking for pDDIs, especially in high risk patients such as cardiovascular patients, and intensive monitoring of patients with predisposing factors, in order to prevent adverse outcomes.

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Barriers and Facilitators for a Mobile App to Report Adverse Drug Reactions and Receive Drug Information: A Focus Group Study

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Introduction: The benefit–risk evaluation of a drug requires a life-cycle approach in both clinical trials and post-marketing studies [1]. In the post-marketing phase, the safety of a drug is mainly assessed via spontaneous reporting. However, a systematic review estimated a median underreporting rate of 94 % for adverse drug reactions (ADRs) [2]. New technologies, such as mobile apps, may stimulate the reporting of ADRs and may provide a tool to communicate on newly discovered drug effects/risks. Currently, it is unknown how patients and healthcare professionals value a mobile app to report ADRs and as a source of drug information, i.e. two-way risk communication.

Aim: To explore the barriers and facilitators of patients and healthcare professionals to using a mobile app for two-way risk communication and to explore their perspectives on a mobile app prototype.

Methods and Results: Focus group discussions with patients and healthcare professionals will be conducted in France, the Netherlands,

Spain and the UK. Furthermore, focus group discussions with pharmacovigilance experts will be conducted in Sweden and Portugal. Patients included in the focus groups will be those with a rare disease or type 2 diabetes and adolescents with any disease. The focus groups with healthcare professionals will include paediatricians, general practitioners, pharmacists, internists and professionals working with patients with a rare disease. Each focus group will consist of around 8 participants and 1-2 researchers who lead the discussion according to a semi-structured interview guide. This interview guide is arranged according to two overarching topics, that is (1) barriers and facilitators for a mobile app on two-way risk communication in general, and (2) opinions about a specific mobile app prototype developed by the WEB-RADR consortium (http://web-radr.eu/). Focus groups will be planned until theoretical saturation has been reached. The discussions will be video-recorded and transcribed verbatim. Inductive thematic analyses will be conducted to arrange the data according to a theoretical-based framework. Currently, data collection is ongoing.

Conclusions: This study will reveal information on potential barriers and facilitators of the uptake of a mobile app on two-way risk communication in general and on the prototype in particular. This information is useful to evaluate the potential value of implementing such an app in practice and to improve the usability of the prototype.

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Drug-Induced Panic Attacks: Analysis of the French PharmacoVigilance Database

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Introduction: To date, there is a lack of data about drug-induced Panic Attacks (PAs). Indeed, the only publications about this topic are isolated case reports.

Aim: The objective of our study was to analyse characteristics of PAs registered in the French PharmacoVigilance Database (FPVD).

Methods: We conducted a retrospective analysis of PAs [MedDRA terms "Panic attacks and disorders" (HLT) or "Anxiety attack" (LLT)] registered in the FPVD between January 1st, 1985 and November 5th, 2014.We excluded cases corresponding to another medical diagnosis or those without sufficient data.

Results: We analyzed 163 cases of PAs out of the 189 registered (26 excluded cases). Mean age of patients was 42 ± 18.6 years, mostly females (63.8 %). A medical history of depression or anxiety was reported for only a quarter (27 %) of patients. A minority (15.3 %) of patients needed to be hospitalized. Almost a third (30.0 %) received a pharmacological treatment for PAs (mainly benzodiazepines) and 11.7 % a psychiatric follow-up. Most of time (85.6 %), evolution was favourable.

Most frequently (n = 136; 83.4 %), PA was directly related to drugs. Generally, PA occurred rapidly after introduction of the suspected drug: the same day in 36.9 % of cases and the same week in 58.8 %. Most of patients (61.8 %) experienced multiple (≥2) PAs.

The most often encountered ATC drug class was "Nervous system drugs" (36.5 %): serotonin reuptake inhibitors (paroxetine, n = 5), antiepileptics (pregabalin, n = 4), smoking-cessation drugs (varenicline, n = 3) and psychostimulants (methylphenidate, n = 3), the second one being "Anti-infectives for systemic use" (12 %, mostly antiretrovirals and antibiotics), followed by "Antiparasitic" (8.8 %, always antimalarial drugs: mefloquine, n = 13), "Respiratory system" (8.8 %, mainly glucocortiocoïds, n = 4), "Alimentary tract and metabolism" (7.5 %, mostly antiobesity drugs: rimonabant, n = 7) and "Dermatologic" (6.9 %, mostly retinoids: isotretinoin, n = 9) drugs.

In 14 out of the 163 analyzed cases (8.6 %), PA was secondary to another adverse drug reaction: mostly an allergy (anti-cancer drugs) or hallucinations (immunosuppressive drugs). Lastly, in 13 cases (8.0 %), PA occurred in a context of a withdrawal syndrome, mainly caused by analgesic opioids, benzodiazepines or antidepressants.

Conclusion: This study highlights that various drugs can induce a PA. Surprisingly, the most often encountered drugs (mefloquine, isotretinoin and rimonabant) are not indicated for a psychiatric pathology. Interestingly, this study also reveals that drug-induced PAs mostly occur in patients without any psychiatric medical history. Lastly, this study shows that PAs can also be triggered by another adverse drug reaction.

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Role of Serotonin 5-HT2C and Histamine H1 Receptors in Antipsychotic-induced Diabetes a PharmacoEpidemiological–PharmacoDynamic study in VigiBase

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Introduction: Pharmacodynamic mechanisms of diabetes induced by antipsychotic drugs remain discussed, while numerous receptors (serotonin 5-HT1A, 5-HT2A, 5-HT2C, histamine H1, muscarinic M3, adrenergic α1, α2 or dopaminergic D2 D3) have been suspected to be involved in the genesis of this Adverse Drug Reaction (ADR).

Aim: To investigate potential relationships between antipsychotics' receptor occupancy (serotonin 5-HT1A, 5-HT2A, 5-HT2C, histamine H1, muscarinic M3, adrenergic α1, α2 or dopaminergic D2 D3 occupancies) and reports of diabetes using VigiBase®, the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database. .

Methods: All ADR reports from 15 first and second generation antipsychotic drugs recorded in the WHO database VigiBase® (from the 1st January 1994 to the 29th March 2013) were extracted. Logistic regression models, completed by disproportionality analysis were used to determine associations between antipsychotics' receptor occupancy and ICSRs of diabetes on VigiBase®. Models were adjusted on age, gender, obesity, duration of drug marketing, exposure to hypo-and hyperglycemic drugs, reporter and geographic area.

Results: During the study period, 94,460 ICSRs involved at least one of the 15 antipsychotics of interest. Diabetes was reported in 1799 (1.9 %) patients. Clozapine was the most frequently reported suspected drug (n = 953; 53.0 %) followed by olanzapine (n = 552; 30.7 %) and risperidone (n = 141; 7.8 %). A significant and positive association was found between histamine H1, Muscarinic M3 and serotonin 5-HT2C, 5-HT2A receptor occupancies and reports of diabetes. A stepwise regression multivariable model showed that only serotonin 5-HT2c (AOR = 2.13, CI 95 % 1.72–2.64) and histamine H1 (AOR = 1.91, CI 95 % 1.38–2.64) predicted the risk for diabetes mellitus ($p < 0.001$).

Conclusions: Using an original pharmacoepidemiology-pharmacodynamic (PE-PD) approach, our study supports that antipsychotic drugs blocking simultaneously histamine H1 and serotonin 5-HT2C receptors are more frequently associated with diabetes reports in VigiBase® than other antipsychotics. These findings should encourage investigation of histamine H1 and serotonin 5-HT2C properties for predicting the risk of glycemic effects in candidate antipsychotics.

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Signals Unmasked for Antipsychotics and Gastrointestinal Congenital Malformations: A study in VigiBase

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Background: Multiple investigations have highlighted the unclear evidence regarding the likelihood of congenital malformations following exposure to antipsychotic drugs during pregnancy. In a previous study exploring competition in signal detection in French spontaneous reporting data, we have investigated the masking effect of Parkinson syndrome reports on signal detection for antipsychotics. Among signals revealed by unmasking procedures, three concerned antipsychotics and congenital malformations.

Aim: As these results were obtained from ancient data (1984-2000), we investigated a potential signal of congenital malformations with antipsychotics using more recent and larger database, VigiBase®, the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database.

Methods: A case/non-case study was conducted in VigiBase®, between 1967 and 2014. Detection of Signals of Disproportionate Reporting (SDRs) were performed using the Proportional Reporting Ratio (PRR) which defines SDRs as drug-reports associations with PRR ≥ 2, $Chi^2 \geq 4$, and number of exposed cases ≥ 3. First, to investigate potentialities of drug competition effects, SDR detection was performed considering the SOC "Congenital, familial and genetic disorders" (SOC congenital) and considering drugs according to the Anatomical Therapeutical Chemical classification level 3. Second, SDR detection for antipsychotics (all combined) was performed for SOC congenital and related HLGT after removing from the database, all reports related to potential drug competitors. Third, it was performed after removing additionally all reports of Parkinson syndrome, a demonstrated event competitor for SDRs related to antipsychotics.

Results: Drug competition analysis using SDR detection for the SOC Congenital and drugs according to ATC level 3 revealed that most SDRs and cases were related to N06A (antidepressants), N03A (antiepileptics) and J05A (direct acting antivirals). No SDR appeared for antipsychotics at this stage (PRR = 0.8; $chi^2 = 17$; n = 1235). Drug competition was handled removing all reports associated to antidepressants, antiepileptics and antivirals from the database. After this, no SDR was found associating antipsychotics to the SOC Congenital or the levels HLGT. After removing reports of Parkinson syndromes, 4 signals appeared : "HLT Palate disorders congenital" [PRR = 2.1 CI 95 % (1.7–3.1); $chi^2 = 30$; n = 41], "HLT Tongue disorders congenital" [PRR = 3.3 CI 95 % (2.2–5.1); chi2=37; n = 25], "HLT Oesophageal disorders congenital" [PRR = 2.7 CI 95 % (1.5–5.0); $chi^2 = 11$; n = 11]"HLT Anorectal disorders congenital" [PRR = 3.0 CI95 % (1.6–5.5); $chi^2 = 13$; n = 11).

Conclusions: After a first signal of congenital malformations with antipsychotics from ancient French spontaneous reporting data, four SDRs for antipsychotics and gastrointestinal congenital abnormalities were unmasked in VigiBase®. To better characterise this potential signal, pharmacoepidemiology studies are needed.

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Atropinic Burden Of Drugs: A New Tool in Pharmacovigilance

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Introduction: Adverse drug reactions (ADRs) and drug interactions of atropinic (antimuscarinic) drugs are frequent and often "serious". Several lists of atropinic burden (AB) were built to investigate prescription. One of them, the Anticholinergic Drug Scale (ADS) classifies drugs according to 4 levels (0 to 3).

Aim and methods: The present study was performed in order to investigate AB in prescriptions according ADS of 3 different populations in France: (1) general population through a survey performed in a community pharmacy between January and April 2013, (2) Alzheimer's disease (AD) patients experiencing ADRs and recorded in the Midi-Pyrénées PharmacoVigilance Database (MPPVD) and (3) patients consulting at the Geriatric Frailty Clinic for Assessment of Frailty and Prevention of

Disability in Toulouse University Hospital between January and October 2013.

Results: In the community pharmacy, among the 2815 prescriptions, 895 (31.8 %) included at least 1 atropinic in 698 patients. Mean age was 40.6 years and most of them (54.3 %) were females. Mean AB was 1.8 ± 1.3 (1-10). Main drugs were H1 antihistamines or antidepressants. In the MPPVD, 475 notifications including at least 1 AD drug were registered. Mean age of the 475 patients was 82.0 ± 7.0 (54–97) years. Mean number of atropinics was 0.9 ± 0.9 according to ADS (0.7 ± 0.9 according to Duran). Mean AB was 1.2 ± 1.5 according to ADS (0.9 ± 1.3, Duran). An AB ≥ 3 was found in 18.3 % of prescriptions according to ADS (11.0 %, Duran). Prescriptions with AB ≥ 3 contained more drugs than prescriptions with AB <3 ($p < 0.001$). There was no association between AB and age.

In the geriatric hospital day population (437 patients, 227 frail-and 210 robust or pre-frail according to Fried's criteria, mean age 83 years), exposure of at least 1 atropinic (found in 16 % of the patients) was associated with frailty (OR = 1.97, 95 % CI 1.10-3.53), independently of polypharmacy. In patients < 85 years, there was an association between AB and frailty (OR for AB ≥ 3 vs 0 = 3.84, 95 % CI 1.43-10.34).

Conclusion: This study underlines the (too) high level of atropinics prescribed (around 1/3 of prescriptions), even in AD (11 %) or geriatric (18 %) populations, where these drugs are not recommended. In older patients, frailty is associated with AB. In pharmacovigilance, AB is a useful tool to suspect potential ADRs and drug interactions and to help drug prescribers to improve quality of their drug prescription.

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Atropinic Burden of Medications During Pregnancy and Psychological Development of the Child: A Cohort Study in EFEMERIS

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Introduction: Drugs with atropinic properties are largely prescribed. Pregnant women are not an exception. Atropinic properties can expose to central nervous system or peripheral adverse drug reactions especially in case of vulnerability (elderly, neonates). We hypothesized that exposure to atropinics during pregnancy could affect development of the fetal nervous system leading to psychological development alterations.

Aim: To investigate a putative association between in utero exposure to atropinics and psychological development during infancy using atropinic burden (AB) scales.

Methods: Women from EFEMERIS, a French database including prescribed and dispensed reimbursed drugs during pregnancy and pregnancy outcomes, who delivered between July 1, 2004 and December 31, 2010 were included (N = 43,740). Each drug was classified as having no (score = 0), small (score = 1) or strong (score = 3) atropinic properties according to Duran list (1). The AB per woman was calculated by adding the atropinic scores of all the drugs prescribed during the whole pregnancy. The AB was categorized into 2 groups: no exposure and score ≥1. Secondary analyses were performed dividing exposure into 4 groups: [0], [1–8], [9–17] and [≥18]. Data for psychological development were extracted from children medical certificates completed at 9 and 24 months. Multivariable logistic regressions were used to assess relations between outcomes and exposure.

Results: During the study period, 34 % (n = 14,925) of women were exposed to at least one atropinic drug. 68 % of them were exposed during the first trimester, 33 % during the second and 26 % during the third. Women with AB (score≥1) were older, had more long-term adverse health conditions, were more frequently smokers or unemployed, suffered more from diabetes, and received twice more drugs during pregnancy than unexposed women. At 24 months, more infants of mothers with AB (score≥1) had problems to "name a picture" [ORa = 1.18 (1.03–1.36)] and to "understand instructions" [ORa = 1.61 (1.13–2.30)] compared to infants of unexposed women. There was no difference at 9 months. Analyses with exposure divided into 4 groups and analyses excluding women exposed to psychotropics (putative confounders) led to similar results.

Conclusion: Atropinics are largely prescribed to pregnant women (around 1/3). Women with atropinics during pregnancy had more comorbidies than unexposed women. Infants of exposed women seem to have lower psychological development at 24 months compared to unexposed ones.

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Improving Adverse Drug Reaction Reporting by General Practitioners in South–West of France

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Introduction: The main limitation of spontaneous reporting of Adverse Drug Reactions (ADRs) is under-reporting, particularly in general practitioners (GPs). In Midi-Pyrénées area, South-West of France, PharmacoMIP network (1) had already shown that regular visits in hospitals by a Clinical Research Assistant (CRA) increase the number of ADR reports. Therefore, we have developed a similar action for General Practitioners (GPs), the main stakeholders of the primary care.

Aim: The aim of this pilot study was to assess the effect of regular visits of a CRA in General Practitioners' (GPs) offices on the improvement of ADR reporting.

Methods: An ADR report collecting system involving regular visits by a CRA has been set up in GPs offices in Midi-Pyrénées area since January 1st, 2015. Firstly, we compared the number of ADRs reported by GPs in the two years preceding the study implementation (2013 and 2014) and since January 2015. Secondly, we compared the characteristics of ADRs registered by the Midi-Pyrénées PharmacoVigilance Center (MPPVC) before and after the setting up of visits by a CRA in GPs offices.

Results: From January 1st, 2015 to May 6, 2015, 256 ADR notifications were reported by GPs, 11.7 % were being "serious". A total of 114 (44.5 %) were directly collected by a CRA in GPs offices. In comparison, 308 ADR notifications were reported by GPs to the MPPVC in 2013 and 287 in 2014. These ADRs accounted for 13.2 and 14.0 % of all ADR reports recorded by the MPPVC during these two last years. Up to now, whatever the study year, no difference was found in the profile of reported ADRs (Table 1).

Table 1 The most frequently reported ADRs by Primary system Organ class, according to the Medical Dictionary for Regulatory Activities (MedDRA)

	General disorders, n (%)	Gastrointestinal disorders, n (%)	Skin and subcutaneous tissue disorders, n (%)
2013	151 (49.0)	81 (26.3)	70 (22.7)
2014	154 (53.7)	70 (24.4)	58 (20.2)
2015*	264 (25.8)	260 (25.4)	184 (18.0)

* Extrapolation to the whole year 2015 from data between January 1st, 2015 and May 6, 2015

Conclusion: These preliminary results showed that regular visits of a CRA in GPs offices have substantially increased the number of ADRs notifications. Assessment of this procedure is on-going to evaluate its effectiveness on a longer period of time.

Reference

1. Gony M, Badie K, Sommet A, Jacquot J, Baudrin D, Gauthier P, et al. Improving adverse drug reaction reporting in hospitals. Drug Saf. 2010;33(5):409–16.

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Information Quality of Adverse Drug Reactions Reported by General Practitioners

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Introduction: Spontaneous reporting of Adverse Drug Reactions (ADRs) remains the cornerstone of postmarketing drug safety surveillance. However, this method shows several limitations like under-reporting or quality of reported information in ADR reports. Incomplete information is a limiting factor in causality assessment. Before promoting spontaneous ADR reporting by GPs, quality of reported information needed to be checked.

Aim: The objective of this study was to assess the information quality in ADR reports sent by GPs to Midi-Pyrénées Pharmacovigilance (PV) Center, South-West of France. Secondly, factors associated with a complete ADR reports could be identified.

Methods: All ADR notifications sent by GPs to the Midi-Pyrénées PV Center from January 1st, 2010 to December 31, 2013 were reviewed. Health care professionals and patients can forward an ADR using either a form online through the website BIP31.fr or "traditional" notifications (i.e. email, letter or fax). A qualitative analysis of information addressed by GPs in ADR notifications was performed. Data required for drug causality assessment were searched in form and free fields. According to information reported in ADR reports (i.e. mandatory variables for a report: date of occurrence, time of onset, clinical description, drugs…), notifications were classified in three groups "well informed", "slightly informed" and "poorly informed". A multivariate logistic regression was performed to research factors which were associated with a "well informed" ADR report. All statistics were made using software SAS® 9.4.

Results: During the study period, 613 ADR reports were analysed. Among these notifications, only 12.7 % were "well informed", with 24.3 % "slightly informed" and 63.0 % "poorly informed". A "well informed" ADR report was associated with a "serious" ADR [OR = 1.70 (1.04–2.76), p = 0.01). ADR notifications using the form online on the website BIP31.fr were not associated with a "well informed" report. No difference according to geographical areas (urban or rural) was found.

Conclusion: The study shows that only 1 out of 8 ADR reports is well documented. Therefore, it appeared important to set up a pharmacovigilance network with GPs, similar to the PharmacoMIP system (1) in hospitals, to promote pharmacovigilance and improve knowledge of data required to assess drug causality.

Reference

1. Gony M, Badie K, Sommet A, Jacquot J, Baudrin D, Gauthier P, et al. Improving adverse drug reaction reporting in hospitals. Drug Saf. 2010;33:409–16.

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Usage Patterns of Single-Ingredient and Combined Analgesic Paracetamol in France

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Background: Paracetamol is one of the most commonly used drugs worldwide, but very little is known of its real-life usage patterns.

Methods: EGB, the permanent 1/97 representative sample from the French national healthcare insurance systems was queried in 2011 to identify usage patterns, concomitant chronic diseases and cardiovascular medication in users of single component paracetamol (SC) and users of paracetamol combined with opiates (CP).

Results: Of 526,108 subjects present in 2011, 338,756 (64 %) had at least one paracetamol dispensation: 277,001 patients (82 %) were dispensed only SC, 61,755 (18 %) CP. SC users were younger (37.9 vs. 50.0 years) with 55 vs 58 % female. SC users had on average 3 dispensations over the year vs. 5 for CP users, for a mean of 28 defined daily doses (DDD, 3 g) of SC vs. 53 DDD for CP; 60 % SC patients bought $\leq$ 14 DDD or less; 11 % bought $\geq$ 60 DDD. Chronic comorbidities were found more often in SC users than in CP users. Use of paracetamol increased with age from about 5 DDD/year below the age of 15 to over 90 DDD/year in patients above the age of 75. The distribution of usage in DDD per year was clearly different between $\leq$45 and >45, with 46 % of patients below 45 buying fewer than 7 DDD per year, whereas 47 % of those above the age of 45 bought more than 28 DDD

Conclusions: Most of the use of paracetamol appears to be short-term, especially for single component paracetamol. These results main help inform on population risks of paracetamol and the need to develop more studies of the potential risks of the drug: even if these risks appear individually small, the sheer size of the user population makes them potentially very relevant from a public health point of view.

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A Population Database Study of Outcomes Associated with Vitamin K Antagonists in Atrial Fibrillation

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Aims: This study aimed to describe the real-life incidence of bleeding, ischemic events and death during prevention of thrombosis in atrial fibrillation (AF) with vitamin K antagonists (VKA), before direct-acting oral anticoagulants (DOAC) were marketed, in France.
Methods Cohort study in EGB, the 1/97 sample of the French national healthcare claims and hospitalization database, of new VKA users with definite or probable AF and no other indication, from 2007 to 2011. **P**respecified outcomes were a composite outcome of death or hospitalization for bleeding, arterial thrombotic event (ATE), or acute coronary syndrome (ACS), and the individual outcomes.
Results: Of 8894 new VKA users in EGB, 3345 had at least probable AF, 51.1 % were male, mean age 75.3; 87.3 % had a CHA2DS2-VASc score $\geq$2 and 11.5 % a HAS-BLED score >3. The incidence rate of the composite outcome was 9.1 per 100 patient-years [95 % Confidence Interval (CI) 8.2–10.0]; bleeding during VKA exposure was 2.8, 95 % CI [2.3–3.4] per 100 PY, including 0.6 [0.3–0.8] cerebral, 1.0 [0.7–1.3] digestive, and 1.4 [1.0–1.7] other bleeds. There were 1.6 [1.2–2.0] ACS, 1.5 [1.1–1.8] ATE, and 3.8 [3.2–4.4] deaths per 100 PY. When patients stopped VKA, the bleeding risk decreased slightly (RR 0.67 [0.43–1.04]), but risk of death or thrombosis increased (RR 3.06 [2.46–3.81] and 1.75 [1.14–2.70], respectively). Non-AF patients had fewer deaths, MI, and ischemic events and similar rates of bleeding events.
Conclusions: This study provides background reference rates for bleeding, ischemic events, and deaths in AF patients treated with VKA before NOAC were marketed.

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Characteristics Associated with Psychotropic Use in a French Cohort of Elderly Farmers

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Introduction and Aim: Living in a rural area could account for some specificities leading to possible differences in what determinants of psychotropic use compared with the general population. Our aim was to evaluate the prevalence and characteristics of psychotropic use (in general and for the main families: benzodiazepines and antidepressants) in individuals living in a rural area of which little was known.
Methods: A cross-sectional study was conducted within AMI, a population-based cohort set up to study the ageing of a rural population.1 Between 2007 and 2009, 1002 subjects aged 65 years and over, living in rural areas in Gironde and retired from agricultural work after at least 20 years of activity, were randomly sampled from individuals registered in the agricultural Health Insurance programme (Mutualité Sociale Agricole, MSA). Analyses by multivariate logistic regression were used to evaluate the characteristics associated with psychotropic use.
Results: The AMI data at inclusion showed a lower prevalence of psychotropic use compared with what had been shown in the general population. This difference was less pronounced for men than women. Results from a multivariate logistic regression highlighted the characteristics associated with use already identified in the general population, such as: female gender, higher age (for benzodiazepines), lower age (for antidepressants), lower life-satisfaction, polypathologies, living in an institution, consumption of other psychotropics for benzodiazepine and antidepressant use. However, some specificities appeared: depressive disorders were more often associated with antidepressant than benzodiazepine use (Odds ratio, OR 3.78, 95 % confidence interval 1.43 to 10.04 versus 1.68, 0.75 to 3.77), anxiety was associated with antidepressant use but not with benzodiazepine use (OR 2.32, 95 % CI 1.17 to 4.62 versus 1.00, 0.65 to 1.55), a higher level of dependency was associated with a higher psychotropic consumption (OR 3.00, 95 % CI 1.05 to 8.60, mainly antidepressants) but with an even lower consumption of benzodiazepines. Finally, cognitive disorders without dementia were associated with an even higher consumption of antidepressants but not of benzodiazepines.
Conclusion: This study highlights a lower use of psychotropics in elderly farmers compared to the general population and an apparently better compliance with good practice guidelines related to benzodiazepine and antidepressant indications.
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Global Mortality Associated with Benzodiazepine Use

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Objective: To assess the putative long-term excess risk of mortality in benzodiazepine users.
Design, Settings, and Participants: A prospective study was conducted in a cohort of elderly people aged 65 years and over, identified among participants in the prospective PAQUID programme [1]. The first 20 years of follow-up of this programme were available for analysis. We first compared prevalent users of benzodiazepines to non-users at inclusion in the PAQUID programme regarding subsequent risk of mortality. Next, we made the same comparison between incident users of benzodiazepines and never users at the first time point (i.e. 3 years after inclusion, T3). Subgroup analyses of benzodiazepine users were conducted in order to evaluate a putative effect of the molecule elimination half-life (long, i.e. $\geq$20 h or short). A Cox model adjusted on the main putative confounders measured at inclusion (T0) in the PAQUID programme (i.e. age, gender, education level, singleness, several variables associated with cardiovascular risk, MMSE, perceived health, depressive disorders and the use of other psychotropics) was used to estimate the Hazard Ratios (HRs) for mortality between groups.

Results: During the 20-year follow-up, 1002 (82.7 %) deaths were confirmed among subjects using benzodiazepines at inclusion (prevalent users) and 2036 (79.4 %) among non-users at this date. During the 17-year follow-up, 182 (82.4 %) deaths were confirmed among incident users of benzodiazepines at T3 and 1087 (74.8 %) among non-users at this date. Prevalent use of benzodiazepines was not associated with an excess risk of mortality (HR 0.99, 95 % CI 0.91 to 1.07) in the model adjusted on the above-mentioned covariates. The same conclusion was true for incident use of benzodiazepines (HR 1.12, 95 % CI 0.94 to 1.32) in the model adjusted on the same covariates. These conclusions remained unchanged when considering the use of long-or short-acting molecules.

Conclusion: We found no association between benzodiazepine use and an increased risk of mortality, whatever the definition considered for exposure (prevalent or incident use, use of long-or short-acting molecule).

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Application of the Case-Population Approach to Vaccine Safety Surveillance

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Introduction: The case-population approach (CPA) compares the degree of exposure to a drug in cases to the overall exposure to this drug in the entire population from which the cases are issued. The exposure to the drug of interest in the entire population can be estimated from the number of drug units sold during the study period and from the defined daily dose for the drug. By using aggregated data to estimate the denominator, this approach can generate in real-time an estimate of the strength of an association, which could be useful in particular to monitor vaccine safety and test urgent safety concerns during vaccination campaign.

Aim: To apply the CPA to vaccine safety surveillance.

Method: In the particular situation of vaccination, exposure in the population is estimated from the number of vaccinated persons and the at-risk period considered for the vaccine-event pair in a given individual. The number of vaccinated persons can be readily computed from sales data and vaccination schedule or from vaccination coverage, and the at-risk period will be defined on a case by case basis according to the vaccine-event pair and the literature data. The CPA was applied to case-control studies (CCS) quantifying risks for influenza vaccine and Guillain-Barré syndrome (GBS) and for A(H1N1) vaccine and narcolepsy that were referred in MEDLINE. Odds ratios (ORs) provided by the CPA were compared to those of CCS.

Results:

Table 1 Comparison of ORs obtained by the case-population approach to those of case-control studies

	CPA, OR (CI 95 %)	CCS, OR (CI 95 %)
Seasonal influenza vaccine and GBS, France[1]	1.3 (0.5–3.1)	1.6 (0.6–4.4)
A(H1N1) vaccines and GBS, France[1]	1.6 (0.2–11.3)	0.8 (0.1–6.3)
A(H1N1) vaccines and GBS, The Netherlands[2]	3.7 (1.4–9.7)	2.5 (0.7–9.3)
A(H1N1) vaccines and GBS, Sweden[2]	3.6 (1.2–10.6)	2.3 (0.5–11.7)
A(H1N1) vaccines and GBS, UK[2]	3.2 (0.7–13.3)	1.3 (0.3–6.4)
A(H1N1) vaccines and GBS, Denmark[2]	5.9 (1.4–25.4)	9.5 (1.7–53)
Influenza vaccines and GBS, Italy[3]	4.8 (3.0–7.8)	3.9 (1.6–9.9)
A(H1N1) vaccines and narcolepsy, France[4]	11.4 (6.8–19.0)	5.5 (2.5–12.0)
A(H1N1) vaccine and narcolepsy, Quebec[5]	1.2 (0.4–3.7)	1.5 (0.4–7.0)

Conclusion: In most situations, CPA association estimates were consistent to CCS ones. The observed disagreement with A(H1N1) vaccine in Sweden and UK could be explained by different levels of vaccination coverage between controls and entire populations, and provide valuable information to further develop CPA.

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Pharmacovigilance Program Results in a Public Hospital Oncology, Experience in Mexico

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Introduction: Oncology is one of the areas of medicine with more active research due to the incorporation of new drugs which frequently come into the clinical setting, and therefore, the safety profile of the products against cancer deserves continuous monitoring. In Mexico since 1995 ongoing pharmacovigilance program was made official, it was not until 2005 after the publication of, "Towards a comprehensive pharmaceutical policy for Mexico", "National model hospital pharmacy" and "Mexican Official Standard 220 pharmacovigilance", which underpin the need of implement pharmacovigilance in public hospitals.
Aim: To show the results and progress after implementation of pharmacovigilance.
Methods: We conducted an analysis of adverse event reports submitted to the national pharmacovigilance centre in the period dec 2012 to may 2015, excluding those regarding to medication errors or lacked conclusive information to be evaluated, all notifications involving character oncology drugs were evaluated based on a specific format that includes national and international guidelines, whereas antineoplastic drugs is already known and reported reactions. A descriptive and observational analysis was performed using indicators of central tendency and dispersion of the general group, a percentile distribution was built, by type of drug associated adverse reaction and outcome events in organs and systems caused by adverse reactions.
Results: Of the 238 notifications, 145 were sent to the national pharmacovigilance centre to be adverse reactions of these; 24 cases were men at an average age of 49.94 ± 12.38 years vs 48.87 ± 12.32 years for 121 women, the most common adverse reactions were of antineoplastic and immunomodulatory drugs with 135 (93.1 %) reports, 4 (2.76 %) reports for the central nervous system, of which 3 were conclusive reports to remove the catalog of drugs to propofol treatment failures and 3 (2.76 %) reports for the digestive system and metabolism, all the reports that were sent were spontaneous case reports, two reports were problems related to improper use of drugs, since at the time of notification there was a method to detect medication errors, 40 (34 %) reports were considered serious adverse reactions.
Conclusion: The implementation of pharmacovigilance in a public hospital contributes to the safe use of drugs, basing policies that guarantee the exercise of pharmacovigilance, and thus contribute to the monitoring of newly marketed drugs and statistics on the Latino population.

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Hospitalisation due to Adverse Drug Reactions in South Africa: A Setting of High HIV and Tuberculosis Prevalence

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Introduction: Worldwide, adverse drug reactions (ADRs) cause approximately 5 % of hospital admissions. However, there is limited data on the extent of the problem from low/middle-income countries, or from settings with high HIV and tuberculosis prevalence. An earlier survey by our group found that HIV infection and antiretroviral therapy (ART) significantly increased the risk of an ADR-related admission.
Aim: We determined the proportion of admissions attributable to ADRs, the drugs implicated in ADR-related admissions, risk factors for ADR-related admission, and the preventability of ADRs resulting in admission, at four hospitals in South Africa.
Methods: We prospectively followed patients admitted to medical wards over a 30-day period and identified suspected ADRs using a trigger tool. A multidisciplinary team performed causality assessment using WHO-UMC criteria. We categorised an admission as ADR-related if the ADR was "possible", "probable", or "certain" and was the primary reason for admission.
Results: There were 1951 admissions involving 1904 patients: the median age was 50 years (interquartile range 34–65), 1057/1904 (56 %) were female, 559/1904 (29 %) were HIV-infected, and 183/1904 (10 %) were on antituberculosis treatment (ATT), of whom 129/183 (70 %) were HIV-co-infected. An ADR was the primary reason for 164/1951 (8.4 %) of admissions. ADR-related admission was independently associated with female sex (adjusted odds ratio (aOR) 1.51, 95 % confidence interval (95 % CI) 1.06 to 2.15), increasing drug count (aOR 1.15 per additional drug, 95 % CI 1.09 to 1.20), increasing comorbidity score (aOR 1.23 per additional point, 95 % CI 1.07 to 1.41) and use of ART for HIV infection (aOR 1.91 compared to HIV-negative and HIV-unknown, 95 % CI 1.17 to 3.11), after adjustment for age and ATT. The most common ADRs were drug-induced renal impairment, hypoglycaemia, drug-induced liver injury, and haemorrhage; with tenofovir, insulin, rifampicin and warfarin respectively the most commonly implicated drugs. Overall, drugs used in the management of HIV and TB were implicated in 56/164 (34 %) of the ADR-related admissions: rifampicin (17 admissions), tenofovir (14), co-trimoxazole (11), efavirenz (9), isoniazid (5), zidovudine (4), stavudine (3), and pyrazinamide (3), and ethambutol, lamivudine, emtricitabine, nevirapine, lopinavir-ritonavir, unspecified ATT and unspecified ART once each. 73/164 (45 %) of the ADRs were considered preventable.
Conclusions: In our survey, 8.4 % of admissions were due to ADRs, a higher proportion than previously found. The range of ADRs and implicated drugs reflect South Africa's high HIV and TB burden. Identification and management of ADRs due to ART, ATT and co-trimoxazole are therefore priority topics for health care worker training programmes.

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Standardized Messaging on Product Packaging as a Mechanism to Mitigate Potential Risks of Medicinal Products with Known Teratogenicity

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Introduction: Effective communication of the known teratogenic potential of medicinal products remains a major issue in protecting the unborn.

Patient awareness regarding the potential risks of some medications in pregnancy is essential to the prevention of major birth defects and miscarriage. Despite the critical nature, there is currently no standardized process to follow, nor language to use, for the labelling of medicinal products in Canada with established teratogenicity.

Aim: To evaluate and compare product packaging to assess the type of risk communication provided to the pharmacists who dispense, and to the patients who receive, medications with known potential to cause fatal harm.

Methods: The U.S. Food and Drug Administration (FDA) website was used to identify drugs with risk evaluation and mitigation strategies (REMS) in place to control for known teratogenic potential. Health Canada's Drug Product Database was then used to establish if identified products were also authorized for market in Canada. Canadian product packaging, excluding the consumer information leaflet, was then reviewed for the type and extent of communication provided to warn against use in pregnancy, including the presence of written language, images and whether or not these were clearly visible until the last dose was consumed.

Results: Product packaging was evaluated for 10 drug products. The packaging for 4 products contained both text and icons, visible until the last dose was consumed, to warn against pregnancy (Accutane™, Pomalyst®, Revlimid® and Thalomid®). Two products, Erivedge® and Toctino®, contained written statements regarding the risk of birth defects, but did not contain visual icons; and the warning for Toctino® did not remain visible until the last dose. Additionally, Erivedge® is supplied in a 28 count bottle thus creating the possibility for repackaging before dispensing. Importantly, 4 products did not contain any written or visual pregnancy prevention warnings on their packaging (Adempas®, Opsumit®, Tracleer® and Volibris®).

Conclusions: There is a lack of standardization to ensure that the risk of teratogenicity associated with certain drugs in Canada is sufficiently mitigated through product packaging. Initiatives to standardize labelling should be explored as a mechanism to reduce or prevent exposure during pregnancy to well-established teratogenic drugs. This investigation involved a small subset of prescription products, however, further research is warranted for products that have the potential to be teratogenic through their mechanism of action (i.e., statins such as simvastatin), and initiatives should extend beyond prescription products to include those available over-the-counter (e.g., Vitamin A).

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Controlled Access Programs as a Mechanism to Mitigate Potential or Identified Medication Risks in Canada

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Introduction: Controlled access programs are increasingly being implemented as a means to mitigate the potential or identified risks of certain medications in order to ensure that the right patient receives the right drug at the right time. Although there are examples of controlled access programs in Canada, there are no regulations in place to govern the need for, or the design and management of, such programs.

Aim: To identify, evaluate and compare individual programs that have been established in Canada to control access to medications for the purpose of minimizing patient risk.

Methods: The Food and Drug Administration website was used to identify drugs controlled via restricted access programs/risk evaluation and mitigation strategies (REMS) in the United States. [1] Health Canada's drug product database was subsequently searched for these same medicines, and labeling was reviewed to assess if these drugs were subject to controlled access in Canada. [2] Identified Canadian programs were evaluated using publicly available information. To allow for comparison across programs, a total of 13 distinct risk minimization activities were predefined and assigned a numerical rating, ranging from 1 to 5. Programs with higher scores had more comprehensive mechanisms in place to control product access and to mitigate for known or potential product risks.

Results: Eight restricted access programs were identified for 11 drug products. The most tightly controlled program was RevAid® (Revlimid®, Thalomid® and Pomalyst®), receiving a total score of 41; 23 points higher than the second most comprehensive program. Rosiglitazone-containing medicines (Avandia® and Avandamet®) scored the lowest (6). Assessing only those programs which included specific pregnancy prevention parameters, RevAid® was again the most tightly controlled (41), followed by Erivedge® (18), Accutane™ (14), and Toctino® (8).

Conclusions: There is no single process in Canada to guide the implementation or management of controlled access programs. Programs that are currently in place vary tremendously in design and in the extent of risk management employed, even when mitigating for the same risk (e.g., teratogenicity).

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Post-Marketing Withdrawal Of Medicines Because of Adverse Drug Reactions: An Analysis of Anti-Obesity Medications

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Introduction: Medicinal products may be withdrawn after regulatory approval when the benefit-to-harm balance is unfavourable. Our objective was to identify anti-obesity medications that have been withdrawn because of adverse drug reactions after regulatory approval, to examine the evidence used to support such withdrawals, to investigate the mechanisms through which the adverse reactions occurred, and to explore the pattern of withdrawals.

Methods: We conducted searches in Pubmed, the WHO database of drugs, the websites of drug regulatory authorities, and selected full texts. We also hand searched references in retrieved documents. We included anti-obesity drugs that were withdrawn between 1950 and 2014. The levels of evidence used for making withdrawal decisions were assessed using the Oxford Centre for Evidence Based Medicine criteria.

Results: We identified 24 anti-obesity drugs withdrawn between 1964 and 2007, 22 of which were psychostimulants. Case reports were cited as evidence for withdrawal in 79 % of instances. Psychiatric disturbances, cardiotoxicity, or drug abuse and dependence accounted for 83 % of withdrawals. The interval between the first report of the adverse reaction and the year of the first withdrawal did not consistently shorten over time.
Conclusions: The use of psychostimulants for treating obesity has not had beneficial effects on the management of obesity over the past 60 years. The shortened interval between first adverse drug reactions and first withdrawal suggests selective reporting in results of clinical trials. Greater transparency in the reporting of harms from drug trials of anti-obesity medications is warranted. Future drug developments should target other mechanistic pathways.

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A Combined Causality Method for Spontaneous Reports of Adverse Reactions on Drugs and Vaccines

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Introduction: An accurate causality outcome is helpful in signal detection. The existing causality methods don't fulfill our practical needs for case-by-case signal detection. They either don't reflect the feelings of the assessor regarding the causality outcome or don't show the underlying arguments. We explored the options for a better method of causality assessment.
Aim: To develop and test a combined causality method for better case-by-case signal detection in the assessment of spontaneous reports of both drugs and vaccines.
Methods: We developed a combined causality model based upon the questions on the Naranjo model [1]. Questions were adapted, removed or added. Each answer results in a score. Unique to this new model is that questions can be excluded if they are not applicable. Causality outcome is based on a percentage that reflects the sum of scores.
In a pilot study we examined the first experiences. In a subsequent study we compared the causality outcome of our new method with the WHO causality method [2], that we considered to be the "gold standard" as well as the Naranjo score [1], the currently used method. Therefore, two couples each assessed 20 selected spontaneous reports of adverse reactions on drugs or vaccines. Within each couple, agreement was reached with an adapted Delphi method. Kappa values were calculated between WHO-versus the new method, and WHO-versus the Naranjo method.
Results: After discussing the experiences of the pilot study, the causality model was adapted. The ranges of the causality outcome were defined. The rate of agreement between the WHO method versus the combined model showed a kappa of 0.48 (drugs) or 0.53 (vaccines), whereas the WHO method versus Naranjo showed a kappa of 0.27 (drugs) and 0.21 (vaccines). The overall impression of the model was positive but in some exceptional cases there was the need of adjustment of the causality outcome.
Conclusion: Based on the kappa values, our combined causality model shows better results than the currently used Naranjo method. As a next step, the new method will be tested in daily practice among all assessors in 100 new reports coming in to our pharmacovigilance centre, with the possibility to adjust the causality outcome with solid argumentation.

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Implementation of the PROTECT Project Recommendations into Signal Detection Processes at the Medicines and Healthcare Products Regulatory Agency (MHRA)

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Introduction: Themed to increase the efficiency and timeliness of signal detection is at the forefront of optimising signal detection in the MHRA's Yellow Card Scheme database. The MHRA is receiving an ever increasing volume of Adverse Drug Reactions (ADR) reports which therefore increases the demand to prioritise work more appropriately using statistical approaches. Results from the Innovative Medicines Initiative (IMI) PROTECT project found that different disproportionality methods gave very similar signal detection performance but the choice of signalling criteria resulted in variability in performance. [1] It was also found that subgroup analyses consistently performed better than stratified analyses [2].
Aim: To evaluate how the results of the PROTECT project will affect routine signal detection processes at the MHRA and determine the optimal signal detection algorithm in our database to maximise both the sensitivity and precision of identifying signals.
Method: Signal detection processes at the MHRA will be evaluated to review the current algorithm. Currently the MHRA uses the Multi-Gamma Poisson Shrinker (MGPS) disproportionality method with the following signalling criteria: EBGM $\geq$ 2.5, EB05 $\geq$ 1.8 and n $\geq$ 3. Stratified analyses are conducted for age, gender and time period, and data are further subgrouped by vaccine/non-vaccine. All elements of this algorithm will be reviewed to find the optimal position for our database.
Results: The PROTECT results support continued use of the mgPS disproportionality method. Our current signalling criteria however shows relatively high precision but low sensitivity and this may not be the optimal position. The routine use of stratified analyses needs to be investigated to determine if a switch to subgroup analyses using the same or different covariates might be appropriate.
Conclusion: The results of the PROTECT project have highlighted number of areas within the current signal detection algorithm used at MHRA that could be optimised. Adjusting the approach to suit the MHRAs database should lead to a more efficient system for detecting potential safety signals enabling the MHRA to take prompt regulatory action when required to help protect public health.

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Adverse Drug Events Identified by Thai ADEs Trigger Tool in Hospitalized Patients in Thailand

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Introduction: Thai adverse drug events (ADEs) trigger tool (Table I) has been developed for measuring ADEs in hospitalized patients recently; however, it has not been evaluated for daily practice.
Aim: To determine the rate of ADEs, and the number of triggers associated ADEs by Thai ADEs trigger tool.
Methods: This is a retrospective study. The data were collected from medical records of hospitalized patients at medical unit in Police General Hospital during June to September 2014. Thai ADEs trigger tool were screened by manual chart review to identify ADEs. Analysis was performed by descriptive statistics as the number of ADEs per 100 admission, ADEs per 1000 patient-days, and the number of positive triggers associated ADEs, including characteristics of positive trigger.
Results: One hundred and thirty patients were reviewed the medical records. Most patients were male (55.4 %) and the mean ± SD age was 63.8 ± 15.56 years. A total of 16 ADEs identified in 12 patients. The rate of ADEs was 12.3, and 10.4 events per 1000 patient-days. Most of ADEs found as category E in 13 events (81.3 %) resulted in temporary harm to the patient and required intervention. Positive triggers for detection of ADEs were identified in 64 out of 702 times (9.1 %). Detail of the number of trigger found and trigger associated ADEs (positive trigger) are presented in Table I.
Conclusion: Thai ADEs trigger tool was able to measure medication-related harm by 12.3 %. Some type triggers and exploring of ADE reporting system should further study in Police General Hospital.

Table I Thai adverse drug events (ADEs) trigger tool, the number of trigger found and trigger associated ADEs (positive trigger)

Trigger	Number of trigger found (times)	Number of positive trigger (times)	Percentage of positive trigger
T1 chlorpheniramine injection	47	12	25.53
T2 hydroxyzine oral	3	1	33.33
T3 steroid oral/injection	36	2	5.56
T4 diagnosis which conclude harm of drug	23	19	82.61
T5 cessation of medication (off or hold)	530	21	3.96
T6 naloxone	6	0	0
T7 Na/Ca polystyrene + drug-induced hyperkalemia	3	0	0
T8 serum glucose <50 mg/dl + drug-induced hypoglycemia	2	0	0
T9 rising serum creatinine + drug-induced nephrotoxicity	21	5	23.81
T10 abnormal liver function test (>2 times of normal upper limit) + drug-induced hepatotoxicity	10	2	20.00
T11 platelet <50,000 + drug-induced thrombocytopenia	8	0	0
T12 AIDS patient with Hct <25 mg %	3	0	0
T13 cancer patient: WBC <3000 cells/μl	10	2	20.00

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Analysis of Patients Admitted to the Emergency Service due to Adverse Reactions to Antineoplastic Drugs in Cancer Center-ISSEMYM

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Introduction: Among the incidents of healthcare we can find failures in the safe use of medicines. These errors do not only have significance from the point of view of the patient's health, but also increase the cost of treatment as they cause enlargement of hospital stay, sequels, diagnosis and further treatment. These incidents are most significant when involves antineoplasic treatment due to this disease requires the use of drugs whose doses vary according to the etiology of the disease and the patient's tolerance as well as low margin of safety.
Aim: Analyse the population who arrived at Continued Health Care service (emergency service) of the Centro Oncológico Estatal-ISSEMYM (COE-ISSEMYM) to identify the percentage of patients admitted for events arising from the use of chemotherapy. Thus we can identify drugs and cancers that produce the highest incidence of serious reactions and thus have the opportunity to create pharmaceutical care strategies that allow us to improve the safety of the therapy of patients.

Methodology: Medical and pharmacotherapeutic profiles of all patients admitted to the Continued Health Care service during the period October 2014 to December, selecting those patients who received chemotherapy before the date of admission to this service. The incidence of different variables as age, gender, type of cancer, reason for admission and type of chemotherapy among others was calculated.
Results: 550 patient were admitted in selected service during the study period, 82 (15 %) of which were derived from the use of some antineoplasic drug. The 84.14 % of these patients corresponding to female patients between 41 and 70 years. The most common cancer was breast cancer and the antineoplasic drug with the highest incidence of adverse reactions were carboplatin, docetaxel and paclitaxel.
Conclusions: Although most of the patients (61.27 %) came to emergency service because of causes typical their own pathology, 15 % of the total admission were by events related to the use of chemotherapy. These results support the need to maintain and enhance the role of the pharmacist in our Center through of different activities like validation of medical prescriptions, intensive pharmacovigilance, identification of medication errors, patienís education. Thus, we can improve de quality and safe in pharmacology treatment.

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False-Positive Pregnancy Tests in Females Receiving Lenalidomide for Treatment of Multiple Myeloma

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Introduction: To manage the teratogenic risk of lenalidomide, the product is available through a restricted distribution program in the United States under the Risk Evaluation Mitigation Strategy (REMS), which requires females of reproductive potential (FRP) to undergo regular pregnancy testing (serum or urine) [1]. Elevated levels of β-human chorionic gonadotropin (hCG) have been observed in several cancers, including multiple myeloma (MM) [2–5].
Aim: To investigate the prevalence of false-positive pregnancy tests among FRP with MM enrolling in the US Revlimid REMS program.
Methods: A search of the Celgene safety database was undertaken to retrieve US cases of elevated hCG among FRP who received lenalidomide from its approval on 27 Dec 2005 through 30 Apr 2014.
Results: Approximately 68,740 females were registered in the lenalidomide REMS program; 5.5 % (3760/68,740) were FRP. There were 97 patients with at least 1 elevated or positive hCG assessed as having false-positive pregnancy tests (ie, the FRP was not pregnant based on follow-up evaluation). This represented 2.6 % of the FRP population.
Conclusions: In a REMS setting requiring regular pregnancy testing of FRP, and more so for patients with malignant disease, false-positive pregnancy tests should be expected, a fact we have underscored previously [1]. There is a need to educate the prescribing community on the phenomenon of false-positive pregnancy tests within pregnancy prevention programs, and we continue to bring this to the attention of healthcare providers [5]. To our knowledge, the prescribing community has not expressed undue concerns about false-positive pregnancy tests, and the fact that these continue to be reported to the company is an indication of compliance with US REMS requirements and the need to prevent fetal exposure to lenalidomide.

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P 133

Evaluation of Thai and Narnajo's Algorithm for Assessing Routine Pharmacovigilance Case Reports Using WHO–UMC Causality Assessment Criteria as Reference

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Introduction: The WHO-UMC causality assessment criteria, the standard method for routine pharmacovigilance (PV) in Thailand, were used much less than Naranjo's algorithm. Whereas, some questions of Naranjo's Algorithm were not able to comply with daily clinical practice and/or were differently interpreted among observers. Therefore, Thai algorithm has been developed [1].
Aims: To evaluate the validity and reliability of Thai algorithm and Naranjo's algorithm for assessing a possible causal link between a drug and an adverse event in routine PV practice using WHO-UMC causality assessment criteria as reference.
Methods: Six hundred individual case safety reports (ICSRs) were randomly sampling from 30 hospitals of Ministry of Public Health stratified by 3 levels of hospital size. A hospital pharmacist with PV qualification was selected to evaluate 200 reports (drug-event pair) collected from each level. Every report was randomly assessed by 3 independent observers and 3 methods. Results expressed as certain/probable probability scores were defined as positive result and assessed for validity and reliability using sensitivity, specificity and Kappa statistics.
Results: A total of 600 ratings for each method were assessed. Comparing with the WHO-UMC methods, Thai algorithm's agreements of positive result were achieved in 361 ratings with a sensitivity of 75.1 %, a specificity of 66.4 %.The assessment using Naranjo's algorithm was similar to Thai algorithm, with 363 agreements of positive result with a sensitivity of 75.5 %, a specificity of 67.2 %. The inter-observer reliability of three observers was quite low. Cohen's kappa value of the WHO-UMC, Thai and Naranjo was 0.33, 0.22 and 0.21 respectively.

Conclusion: Thai algorithm and Naranjo's algorithm had similar sensitivity and specificity for assessing ICSRs in daily practice, using the WHO-UMC causality assessment criteria as reference.

Keywords: Pharmacovigilance, Thai algorithm, Naranjo's algorithm, WHO-UMC causality criteria

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Characterization of Fatal Adverse Drug Reaction of Spontaneous Reporting in the Thai Vigibase

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Introduction: In 2014, suspected adverse drug reaction (ADR) of spontaneous reporting in Thailand found 9670 serious ADRs (20.76 %). In seriousness criteria, cause and/or prolongation of hospitalization were mostly found (84.80 %) but ADR resulting in death was the most seriousness and impact. Fatal ADR should be explored.

Aim: To characterize of fatal ADR of spontaneous reporting in the Thai national pharmacovigilance database (Thai Vigibase).

Methods: Suspected ADRs with resulting in death reported to the Thai Vigibase by spontaneous reporting system from 1st January to 31st December 2014 were reviewed and analysed. Descriptive statistics and signal validation were performed.

Results: A total of 46,590 spontaneous reports were received by the Thai Vigibase between January and December 2014, of which 139 cases (0.30 %) were serious adverse event with resulting in death. In total fatal outcomes, 76.98 % attributed to adverse event, with 24 cases (17.27 %) may be associated with health product, and 5.75 % were unknown. Ages of the patients ranged from 9 to 96 years, with a mean age of 59.92 ± 16.10 years old, 37.4 % were male and 30.2 % were not specified. Body as a whole-general disorder according to system organ class was mostly found (31.68 %), followed by resistance mechanism disorder (14.17 %) and skin and appendage disorder (10.63 %), respectively. Antineoplastic and immunomodulating group was mostly submitted (74.4 %). The most commonly used drug was rituximab. Of these, we found 254 drug-adverse event pairs. 233 drug-AE pairs were known ADR, such as allopurinol-Stevens-Johnson syndrome (SJS), bortezomib-thrombocytopenia, erythropoietin alfa-aplasia pure red cell and simvastatin-rhabdomyolysis. 21 drug-AE pairs were unknown ADR. Some new events were cyclophosphamide-pneumonia, doxorubicin-respiratory distress, rituximab-septic shock, and prednisolone-sepsis. All unknown ADRs were validated by the Safety Signal Assessment Working Group. All of them were false signals because of disease progression and many suspected drugs.

Conclusions: The majority of fatal ADRs of spontaneous reporting were known ADR. All unknown ADRs were false signals. However, some known ADRs in this study are preventable, e.g. pure red cell aplasia association with erythropoietin alfa. Thus, appropriate risk management plan should be taken to reduce the risks and to enhance patient safety.

Further sources of information/Reference

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Sources of Literature in Pharmacovigilance

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Introduction: There are a large number of publications on safety monitoring of medicinal products, published in different languages from all over the world.

Aim: Publications on pharmacovigilance and drug safety are aimed to assure the safety of medicines by ensuring reliable and timely exchange of information on drug safety issues. It helps in promoting pharmacovigilance activities both at national and international level, encouraging participation essentially to build up WHO Programme for International Drug Monitoring.

Methods: Many texts were developed in consultation with WHO Collaborating Centre for International Drug Monitoring and National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. In addition, several publications also came into existence by individual scientists, national and international societies working in the field of Pharmacovigilance. These publications are widely circulated and intended for wide-ranging readership for policy makers at all levels of healthcare, particularly those concerned with drug policy; staff and consultants in national drug regulatory authorities; healthcare practitioners including doctors, nurses and pharmacists; pharmaceutical industry executives and scientists; professional staff in national Pharmacovigilance centres; editors of medical and scientific journals; health epidemiologists; health economists; professional staff of poison and drug information centres; health administrators; consumer groups and patient support groups; legal advisors in health care; schools of health sciences, and the concerned layperson, etc.

Observations: In the present talk, authors would like to compare number of publications in the form of books and periodicals by Indian and Non-Indian authors in addition to publications by professional organizations such as UMC-WHO Collaborating Centre for International Drug Monitoring, National Pharmacovigilance Centre, International Society of Pharmacovigilance (ISoP) and Society of Pharmacovigilance, India (SoPI).

Conclusion: The significance of sources of literature in pharmacovigilance cannot be ignored in an era where so much importance is being given to the safety of medicinal products. A separate section on pharmacovigilance publications is needed to be developed. The source of the above literature discussed in the present paper is mostly derived from the library of Ibn Sina Academy, Aligarh, India.

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Are We Delivering Safe Intravenous Opioid Infusions in Paediatric Patient?—Evaluation of the Current Practice in a UK Paediatric Hospital

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Introduction: Opiate intravenous infusions are the therapy of choice in severe pain. However, administering infusions to children requires complex dosage calculations, rate adjustments and often multiple manipulations of injectable medicines to obtain the final "ready to use" solution for both continuous infusion and additional boluses; potentially putting children at high risk [1-2].
Aim: To investigate the practice and accuracy of healthcare professionals (HCPs) in theatres and wards when preparing morphine infusions for nurse/patient controlled analgesia (N/PCA) use for inpatients in a UK children's hospital.
Methods: A mixed methods study in which direct observation of HCPs preparing paediatric morphine infusions for N/PCA in theatres and on wards; also focus groups with HCPs and quantitative analysis by UV-Vis Spectrophotometer of a sample of syringes. The British Pharmacopoeia (BP) reference limits of ±7.5 % were used to compare morphine labelled strength (LS) with actual syringe concentration.
Results: The preparation of 153 syringes was observed which related to 128 paediatric patients [mean age (±sd) 7.5 years ± 5.6; 65.3 % male]. 64 % (98/153) were prepared by anaesthetists in theatres, 36 % (55/153) by nurses at ward level.
Major differences in preparation methods were identified. The final volume prepared was above the required volume (50 mL) in 35.9 % (55/153) preparations. Wearing gloves during preparation was not followed in theatre for 83.7 % (82/98) of syringes. No decontamination of morphine ampoules was undertaken during preparation of any syringe. Inconsistency in the appropriate syringe size used to withdraw drug from the ampoule was observed in both theatres and wards. Lack of appreciation of the overage in morphine ampoules by HCPs was identified. Of the syringes analysed 61.5 % (48/78) had a concentration outside the BP reference limits (92.5–107.5 % LS), most were in excess (83.3 %, 40/48); 12.5 % (10/78) deviating by more than +20 %, one deviated by 100 %.
Conclusion: This study identified that variation in preparation techniques followed by HCPs may result in morphine N/PCA dosages that are significantly higher or lower than that prescribed. Also, a lack of understanding of ampoule overages, accuracy of the syringe size used, dosage calculations and ability to measure small volumes led to inaccurate concentrations in prepared infusions.

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Comparison of Adverse Events Between Drugs and Consumer Goods as Collected Within a Spontaneous Reporting System

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Introduction: The regulatory pathway for over the counter (OTC) drugs/medicines differs from consumer goods, including more stringent post-market safety surveillance. However, consumers using OTC drugs do not necessarily consider them to be 'real drugs' with safety profiles different from consumer goods used in a similar fashion. Our company manufactures numerous products across regulatory classifications. We assess consumer complaints within a single spontaneous reporting system (SRS) across products and are able to ascertain whether consumers have comparable adverse event (AE) profiles across and within product categories.
Aim: To explore differences and similarities between OTC drugs and consumer goods within our SRS.
Methods: We conducted a descriptive analysis of SRS July 2013-June 2014. Outcomes were defined by MedDRA preferred terms (PTs) and system organ classes (SOC).
Results: There were 2142 drugs and 6351 consumer goods in product categories containing drugs. There were 31,437 AE cases with 67,431 PTs among drugs and 44,021 AE cases with 303,299 PTs among consumer goods. Consumers reporting cases for drugs were more likely to be male, elderly and live in North America, than with consumer goods. The proportion of serious cases was similar between drugs and consumer goods. Among all ingested products, 68 % of AE cases were for drugs. Specific examples by product category are noted within the table. For both drugs and consumer goods, the most common PTs in product categories for ingested products were related to product use (e.g., off label) and underlying conditions (e.g., diarrhea for stomach remedies). Among all products used on the skin or mucosal tissue, 27 % of AE cases were for drugs. For both drugs and consumer goods, the most common PTs in these product categories were for dermatologic conditions.
In some, though not all, product categories, AE cases were reported more often for drugs. The types of PTs differed by product category, but were comparable between drugs and consumer goods within product categories. Assessment by SOC yielded similar results.
Conclusions: Drugs and consumer goods within a product category had similar AEs in our SRS. Further exploration is warranted to better understand what we anticipate to be a multifactorial relationship between risk profiles and consumer expectations for these products.

Table 1 Proportion of drugs within select product categories

Example product category	Products (% drugs)	Cases reported (% drugs)	PTs (% drugs)
Oral care (ingested)	492 (57)	17,436 (52)	39,112 (50)
Female hair care (skin/mucosal)	2093 (26)	9047 (45)	23,850 (40)
Antiperspirants, deodorants, and body spray (skin/mucosal)	710 (76)	4334 (74)	9.778 (77)

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A Qualitative and Quantitative Review of Additional Risk Minimisation Measures for EU Centrally Authorised Products, 2006–2014

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Introduction: Guidance on risk management plans (RMPs), which include risk minimisation, was first released in the EU in 2005 and updated in 2012. Specific guidance on risk minimisation was issued in 2013.
Aim: To assess the impact of risk minimisation interventions we conducted a qualitative and quantitative review of the European Public Assessment Reports (EPARs) for the study period 2006-2014.
Methods: All New Chemical Entities (NCEs) with initial EU Commission Decision granted marketing authorisation between 1/1/2006 and 31/12/2014 were identified; generic products were not included. The number and percentage of NCEs with additional risk minimisation measures (aRMMs) were computed by calendar year and stratified by target population and type of intervention. Associated risks and measures of effectiveness were also reviewed.
Results: The EPAR database encompassed 627 medicines, including 481 NCEs authorised during the study period. The NCEs authorised with aRMMs varied from a minimum of 12.2 % (6 of 49) in 2008 to a maximum of 40.6 % (13 of 32) in 2010. No clear trend over time was observed. Among NCEs with aRMMs (n = 125), those in the antineoplastic and immunomodulating ATC category where the most frequent (26.4 %, 33 of 125). Throughout the study period aRMMs were more common among orphan medicines, biological products, medicines authorised under exceptional circumstances or with conditional approval.
All aRMM consisted of an educational programme, with 13.6 % (17 of 125) also including a controlled distribution or access plan. Only 4.0 % (5 of 125) aRMMs included a pregnancy prevention programme. Educational interventions mostly targeted healthcare professionals (97.6 %, 122 of 125), with 8.0 % (10 of 125) targeting pharmacists. Patients were targeted in 50.4 % (63 of 125) of aRMMs; however their involvement consistently decreased throughout the study period from 88.9 % (8 of 9) in 2006 to 41.7 % (5 of 12) in 2014.
Measures of aRMM effectiveness were inconsistently and poorly described. Since 2012 there has been an increase in the number of drug utilisation studies and surveys of healthcare professionals and/or patients.
Conclusion: This review shows that between 2006 and 2014 a quarter of NCEs were approved in EU subject to aRMMs. Most consisted of educational interventions; and patients were targeted less over time. The new legislation does not appear to have had an impact on the number of approved NCEs with aRMMs, target population or type of interventions. However, since 2012 the evaluation of the effectiveness of aRMMs appear to be more carefully planned based on qualitative review.

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Application of the International Society on Thrombosis and Haemostasis (ISTH) Classification of Major Bleeds Within a Post Authorization Safety Study

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Background: Haemorrhage is a frequent complication of anticoagulant (AC) use. In order to compare incidences between trials a definition of major bleeds (MB) in non-surgical studies was developed by the International Society on Thrombosis and Haemostasis (ISTH) in 2005. In recent years, the Committee for Medicinal Products for Human Use (CHMP) has recommended its use in studies for prevention of stroke and systemic embolic events (SEE) in patients (pts) with non valvular atrial fibrillation (NVAF) and prevention of deep vein thrombosis (DVT) and pulmonary embolus (PE). Bleeds reported in a Specialist Cohort Event Monitoring (SCEM) study on the oral AC rivaroxaban (conducted as part of Risk Management Plan) will be classified using this definition
Objectives: To describe the methodological considerations of applying this definition to observational data
Methods: Aim to collect data on 1700 pts treated for the prevention of SEE [n = 561], and the treatment and prevention of recurrent DVT and PE [n = 1005]. Recruitment Sep2013-2016. Information (info) was obtained on bleeds that occurred during initial 12 weeks; criteria for MB included: a fall in Hb of $\geq$ 2 g/dL, a transfusion of $\geq$ 2 units, critical organ site, or fatal outcome. Bleeds will be classified as clinically relevant non major (CRNM) if none of the MB criteria were met, but if medical attention was required and/or a change in antithrombotic therapy and/or any other bleed with clinical consequences
Results: To minimise misclassification, supplementary info will be used to validate and confirm the type, obtain missing data and further details of the bleed (site, management, and outcome). All bleeds will be adjudicated by an expert, and interim results will be published
Conclusions: By systematically applying the ISTH definition, we hope to gain better understanding of the type of bleeds reported in a cohort of AC users, associated risk factors and outcome details. This should enable more meaningful comparisons to be made between major and CRNM bleeding incidences obtained in this setting with those observed during trials

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Development of a Qualitative Method to Assist in Interpretation of Results from Disproportionality Analyses in the SAFEGUARD Project

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Introduction: Disproportionality analyses are used in spontaneous reporting systems to support signal detection. Limitations of these systems, however, present challenges for interpretation and comparisons with

other types of data. The purpose of this study was to develop an output suitable for integration with other data, specifically epidemiological studies investigating the safety of diabetes drugs in the context of the SAFEGUARD project.

Aim: To categorise associations from disproportionality analyses in the SAFEGUARD project and assess their level of uncertainty.

Methods:

- Disproportionality analyses were performed for 29 diabetes drugs and 9 outcomes of interest using 8 different strategies: two databases (FAERS and Eudravigilance), two outcome definitions (broad and narrow) and two reference groups (all drugs and diabetes drugs only).
- An algorithm was defined, depending on which analysis strategies detected disproportionality, to categorise each drug-outcome pair (n = 261) as low, medium, high or unclear evidence of association.
- Each categorisation was qualitatively assessed using 9 'uncertainty factors': (1) specificity of outcome definition, (2) potential for stimulated reporting, (3) time on the market, (4) consistency between databases, (5) multiple testing, (6) reporter status, (7) level of drug use, (8) masking bias and, (9) use of statistical thresholds.
- An overall 'uncertainty score' for each categorisation from 0 (low uncertainty) to 1 (high uncertainty) was derived from the proportion of the 9 uncertainty factors that applied.

Results: Twenty-three pairs (8.8 %) were classified as high evidence of an association, 48 (18.4 %) as medium, 122 (46.7 %) as low and 68 (26.1 %) as unclear. Examples of those categorised as 'high' are shown in Table 1.

Table 1 Examples of pairs categorised as 'high' evidence of association with their uncertainty scores

Drug-outcome pair	Uncertainty scores
Incretin-based therapies and pancreatic outcomes	From 0.25 for liraglutide to 0.63 for vildagliptin
Glitazones and heart failure	0.57 for pioglitazone; 0.14 rosiglitazone
Pioglitazone and bladder cancer	0.14
Rosiglitazone and cardiovascular outcomes	0.14

Conclusion: Disproportionality analyses should be interpreted in the context of their limitations due to potential biases in the data. We have used an uncertainty score, as a measure of these limitations, to qualify the categorisation of the associations detected. The assessment criteria were not exhaustive, were topic-specific and required considerable computation. Thus further refinement and evaluation is required before such methods could be recommended for routine use. Nevertheless the categorisation and uncertainty score provide an output that can be compared and integrated with similarly formatted results from independent studies.

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Applying the Ready Reckoner Tool for Assessing Antipsychotic Prescribing Within a Post-Authorisation Safety Study

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Introduction: In the UK, the Ready Reckoner algorithm is a tool used in psychiatric clinical practice to monitor antipsychotic dosing in patients with complex antipsychotic regimens. For each patient, the dose of each antipsychotic can be converted to percentage of relevant maximum dose according to each indication and titration stage as specified in the Summary of Prescribing Characteristics (SPC). Total dose percentage (TD %) >100 % identifies patients at risk. A nested case control (NCC) study was undertaken as part of a post authorisation safety study (PASS) program to explore possible dose-event response for somnolence/sedation (SS) after starting a new formulation of an antipsychotic, with a focus on evaluating total daily dose (TDD)> 600 mg.

Aim: An exploratory analysis to evaluate use of the Ready Reckoner algorithm as an alternative indication-adjusted dose metric to model antipsychotic treatment effects.

Methods: An incidence density matched NCC study used data from a primary care based observational cohort study (N = 13,276) identified between September 2008 and February 2013. Of 756 cases, 212(28 %) were randomly selected and 170 risk sets created. For all subjects, the reported TDD (start, maintenance, and event) were converted to TD % in accordance with the Ready Reckoner algorithm; for off label indications the SPC dose range for major depression was used. Fractional polynomial (FP) logistic models explored functional form; empirical and fitted within-person Ordinary least Squares (OLS) dose trajectories described patterns over time.

Results: SS cases tended have higher reported TDD vs controls at start [median 300 (IQR 200,600) vs 200 mg (IQR 100,300), $p < 0.01$] but the inverse was seen when the TD % metric was applied (median 50 % (IQR 16,100) vs 75 % (33,100), $p = 0.02$). At maintenance and event, similar relationships were observed for reported TDD and TD % variables. SS risk was a negative function of TDD and TD %. No deviation from linear assumption was apparent for start and maintenance doses (FP2 vs linear, P>0.05), but was non-linear for TD % at event ($p = 0.04$). In exploring pattern over time, the general trend was decreasing for both cases and controls, although slower for controls.

Conclusions: This exploratory analysis demonstrates the feasibility of the Ready Reckoner algorithm as an alternative method of calculating an indication-adjusted variable suitable for analysing dose-related effects, particularly where multiple indications may exist that use various dose ranges. Analytical advantages include avoiding creation of strata of small sample sizes. Limitations include possible metric under-estimation from missing data for other concomitant antipsychotics.

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Potential for Underdosing of Antipsychotics in Primary and Mental Health Care: Findings from Post-Authorisation Safety Studies on Seroquel XL©

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Introduction: UK guidelines state that the lowest possible dose of antipsychotics should be used and titrated to the lowest effective dose. A risk management plan of quetiapine extended release (Seroquel XL©) had a need to describe long-term (12+ months) and short term (12 weeks) use and safety in primary and mental-health care setting, respectively. An M-PEM study monitored use and safety in all indications. A SCEM study monitored early-onset use and safety during Seroquel XL© titration and at higher doses (>600 mg) in Schizophrenia and Bipolar Disorder adults (>18 years); a comparator group (immediate release quetiapine) was also included (ENCEPP Study 5412). M-PEM and SCEM study objectives included exploring posology.
Aim: An adhoc analysis to describe prevalence of potential underdosing in clinical practice.
Methods: Exposure, selected prior medical history and medications use data were collected for each study from forms sent to hospital specialists for SCEM December 2009 to December 2012 and to primary care physicians (GPs) for M-PEM September 2008 to February 2013. Descriptive statistics were calculated; doses were converted to percentage of relevant maximum dose according to each indication and titration stage as specified in the Summary of Prescribing Characteristics (SPC).
Results: In the M-PEM cohort (N = 13,276), at start of treatment potential underdosing was calculated for: 37 % (785/2136) Schizophrenia patients, 3 % (98/3500) Bipolar Disorder patients, and 6 %(147/2646) patients with Major Depressive Disorder. At date maintenance treatment regimen was reportedly achieved, potential underdosing was calculated for 38 % (509/1339) Schizophrenia patients, 33 % (721/2165) Bipolar Disorder patients, and 32 % (531/1648) with Major Depressive Disorder. In the SCEM XL cohort (n = 646), at start of treatment potential underdosing was calculated for 56 % (144/258) Schizophrenia patients and 59 % (204/345) Bipolar Disorder patients. At date maintenance treatment regimen was reportedly achieved, potential underdosing was calculated for 86 % (223/258) Schizophrenia patients and 91 % (315/345) Bipolar Disorder patients.
Conclusions: Both studies found that potential underdosing occurred very commonly in all indications studied. Start dose data correlated poorly with SPC and expert guidelines to use lowest effective dose, but corresponded to UK prescribing guidelines which do not recommend excessive doses, unless other evidence–based strategies have failed. Possible explanations for more common potential underdosing in SCEM vs M-PEM is that patients treated by specialists may require more individualised therapy (including use of immediate release quetiapine) to initially stabilise their condition, whilst GPs tend to manage patients at later stages. Further work will explore impact of age and prior/concurrent psychotropic use on underdosing.

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Antipsychotic Use in Older Adults with Dementia: Results from a Post-Authorisation Safety Study

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Introduction: The UK National Institute for Health and Care Excellence recommends that antipsychotics can be used in elderly patients under strict guidelines, however use is associated with serious safety concerns [including cerebrovascular accidents (CVA)]. A Modified Prescription-Event Monitoring (M-PEM) study was conducted as part of the Risk Management Plan for Seroquel XL© to examine it's safety and use, irrespective of indication, as prescribed in primary care in England.
Aim: An adhoc analysis to examine the risk of CVA in the elderly.
Methods: M-PEM uses an observational cohort design; data on exposure were derived from dispensed prescriptions that had been issued by primary care physicians (GPs) between September 2008 and February 2013; data on events were derived from forms completed by GPs sent 12+ months after the date of each patient's first prescription. Age and sex adjusted Mantel-Haenszel Odds Ratios (ORs) plus 95 % Confidence Intervals (CI) were calculated for all cause deaths and CVA (MedDRA PT: CVA, Cerebellar infarction, Cerebral haemorrhage, Haemorrhagic stroke) in elderly patients with or without dementia, and with or without psychosis.
Results: Final elderly cohort comprised 3127 patients; median age 77 years (IQR 69,84); 62 % (n = 1940) female; 29 % (n = 892) had indications associated with dementia, of which 17 % (n = 148) had concomitant psychosis. Within 12 months of starting Seroquel XL© 10 % (n = 301) died; commonly from bronchopneumonia (n = 44). Deaths were more likely in elderly with dementia than without [15 % (136/892) vs 8 % (165/2070); adjOR 1.5(1.2, 1.9)] but not for dementia patients with psychosis versus those without [14 % (21/148) vs 15 % (115/744); adjOR 1.0 (0.6, 1.6)]. At least one report of CVA was reported in 23 (<1 %) elderly patients, of which 17 had a fatal outcome. CVA events were twice as likely as in patients with dementia than without [48 % (11/23) vs 28 % (881/3104); adjOR 2.8 (1.3, 6.2).
Conclusions: Approximately one-third (29 %) of this elderly cohort had dementia with or without psychosis. A higher rate of death was observed in elderly patients with dementia than without, but concomitant psychosis with dementia did not appear to be a risk factor. CVA was uncommon (<1 %), but more likely in elderly with dementia than those without. Study limitations include low CVA counts, possible misclassification of depression and delirium as dementia and limited information on other possible factors (other modifiable medical and environmental factors).

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Defining Risk Profiles in Special Populations-Results from a Post Authorisation Safety Study of Seroquel XL© Conducted in England

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Introduction: A risk management plan of quetiapine extended release (XL) had a need to describe use and monitor long-term (12+ months) safety in the primary care setting. Its aim was to monitor for known risks (e.g. metabolic effects) and safety signals in patients of all indications. One of the study objectives included monitoring specials populations who may be more vulnerable to risks due to past medical history and/or concurrent conditions or medication use.
Aim: To describe risk profiles of special population groups (by indication, past medical history, prior psychoactive drugs, and age ≥65,<64 years).
Methods: An observational, single-exposure cohort design. Data were derived on exposure from dispensed prescriptions; on events from forms completed by physicians 12 months post first exposure. For general

surveillance crude incidence densities (ID) per 1000 patient-months were calculated for events in months (m) 1, m2–6, m7–12 and m1–12 inclusive for cohort, and by special population group. Overdose events were grouped by suicidal ideation, suicidal behaviour, self-injurious behaviour. Event ID differences (IDD m1–m2–6) +95 % CI excluding the null (0) were signals of starting treatment. Survival methods estimated rates of overdose and hyperglycaemic events (+95 % CI) per 1000 patient-months (where n>7 and excluding patients if event dates were missing).

Results: Cohort comprised 13,276 patients; 59 % female; median age 43 (IQR 33,55). Events with highest ID m1-12 inclusive were: Sedation, n = 317: ID 40; Somnolence,n = 288: ID 47; and Weight increased,n = 198: ID 54. Somnolence and Sedation were associated with starting treatment overall (IDD m1–m2–6: 3.8 (1.5, 5.7) and 2.5 (0.8,4.2) respectively) and in special population groups with Bipolar Bisorder or Non-licensed (off-label) indications; age ≤64 years; and a history of depression. For hyperglycaemic events, the highest rates in months 1-12 inclusive were: raised random blood sugar (n = 122):1.0 (0.8, 1.2) and raised fasting plasma glucose (n = 104):0.8 (0.7, 1.0). Patients with a history of impaired glucose tolerance and diabetes appeared to have highest rates of hyperglycaemic events. Of 104 overdose events, a history of mental illness was reported for all patients; event rates in months 1-12 inclusive were: suicidal behaviour (n = 84):101.8 (82.2126.1), suicidal ideation (n = 1):4.0 (0.6, 28.4), and self-injurious behaviour (n = 15): 36.6 (22.0, 60.1).

Conclusions: For frequently reported central nervous system, psychiatric and hyperglycaemic events, many patients had pre-existing risk factors that are likely to put them at elevated risk. This study demonstrates the ongoing importance of observational studies to support the risk: benefit evaluation of medications.

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Observational Assessment of Safety in Seroquel (OASIS)—Rates and Patterns of Common Events

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Introduction: The Observational Assessment of Safety in Seroquel (OASIS) study (ENCePP Study reg. 5412) aimed to extend the post-authorisation safety knowledge of quetiapine extended release (Seroquel XL©) in the mental health secondary care setting, as prescribed by psychiatrists in new user adult (>18 years) patients with Schizophrenia or Bipolar Disorder compared to quetiapine immediate release (IR). The primary focus was on short-term (12-week) safety and high dose (>600 mg/day) use.

Aim: To quantify event incidence and pattern after starting treatment and compare common event rates between users defined by dose and formulation

Methods: An observational cohort design using Specialist Cohort Event Monitoring (SCEM). Questionnaires completed by specialists collected data on patient characteristics, exposure and events between December 2009 and December 2012. Exposure (patient-weeks) was calculated for: total cohort and sub-group stratified by formulation. Period specific exposures were calculated for three 4-week periods for total cohort. Period specific exposures were further stratified by formulation and high dose use (where >600 mg/day for >50 % of each 4-week period). Crude event Incidence Densities (ID) per 1000 patient-weeks and ID differences (IDD +95 % CI) were calculated within and between groups over total study period and 4 week exposure periods; IDD 95 % CI excluding the null (0) were considered signals of events associated with starting treatment and/or high dose.

Results: SCEM cohort comprised 845 patients; 471 (59 %) were female and median age was 39 years (IQR 29, 49); 40 % (n = 338) had Schizophrenia, 52 % (n = 442) had Bipolar disorder; 8 % (n = 65) had Other indications. High dose use was reported for 4 % (28/631) in XL group and <1 % (3/214) in IR group. The most frequently reported events weeks 1-12 inclusive (not associated with indication) were: sedation:ID 24, somnolence:ID 20, akasthesia: ID 3, and parkinsonism: ID 2. In the XL group, the IDDs for these 4 events were non-significantly lower for high vs standard dose for total study period and weeks 1-4. Within XL high dose group, sedation and somnolence were associated with starting treatment (IDD w1–4 to w5–8 : 25 (7, 42) and 14 (14, 15) respectively); this pattern was also observed within XL and IR standard dose groups. Low counts in high dose group and IR cohort precluded reliable comparisons.

Conclusions: This study found that sedation and somnolence were common events associated with starting treatment, but not with high dose. Although the frequency of high dose use was low, OASIS provides important information on the safety and utilisation of Seroquel XL©.

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Use of Antipsychotics in Mental Health Secondary Care Setting Versus Primary Care: Results from Two Post-Marketing Safety Studies

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Introduction: Generalisability of results from Modified Prescription-Event Monitoring (M-PEM) studies conducted in primary-care may be limited by excluding patients with complex characteristics (underlying/concurrent disease, medications) exclusively managed in hospital. Specialist Cohort Event Monitoring (SCEM) applies to secondary care. A risk management plan of quetiapine extended release (XL) had a need to describe use and monitor long-term (12+ months) and short term (12 weeks) safety in primary and secondary care, respectively. An M-PEM study monitored safety and use (all indications). A SCEM study monitored early-onset events during titration and at higher doses (>600 mg) in Schizophrenia and Bipolar Disorder adults (>18 years) for whom the decision to treat was made by psychiatrists; a comparator (immediate release (IR) quetiapine) was included (ENCEPP Study 5412).

Aim: To explore the potential of bias by comparing M-PEM and SCEM patient characteristics.

Methods: Both studies used an observational cohort design. MPEM data derived from dispensed prescriptions September 2008–February 2013 and

questionnaires sent to GPs 12+ months after each patient started treatment. SCEM data derived from questionnaires completed by psychiatrists 12+ weeks after each patient started treatment December 2009–December 2012. Descriptive statistics and Odds Ratios (OR) +95 % CI (exact method) were calculated.

Results: SCEM XL cohort (n = 646) included 258 (39.9 %) with Schizophrenia, and 345 (53.4 %) with Bipolar Disorder. M-PEM cohort (n = 3276) included 2362 (17.8 %) adults with Schizophrenia, 3820 (28.6 %) with BD. In Schizophrenia, SCEM patients were significantly more likely than M-PEM patients to be <30 years old [84 vs 488; OR 1. (1.2, 2.2)], have a history of: depression [152 vs 446; OR 6. (4.8, 8.1)], extrapyramidal symptoms (EPS) [46 vs 103; OR 4. (3.2, 7.0)] and prior antipsychotic use [175 vs 779; OR 4.2 (3.2, 5.6)]; recent (<28 days prior) IR use was less likely [18 vs 632; OR 0.2 (0.1, 0.3)]. In BD, SCEM patients were more likely than M-PEM patients to have a history of: depression [258 vs 1344; OR 5. (4.2, 7.0)], EPS [34 vs 66; OR 6.2 (3.9, 9.7)], diabetes [37 vs 168; OR 2.6 (1.7, 3.8)] and prior antipsychotic use [182 vs 772; OR 4.4 (3.5, 5.5)]; recent IR use was less likely [17 vs 985; OR 0.2(0.1, 0.2)].

Discussion: SCEM patients had a higher prevalence than M-PEM patients of depression, EPS, diabetes and antipsychotic use which are risk factors for some adverse events. Considerations include differences in: the data available within medical records; prescribing guidelines; method of identifying patients; and overlap of study populations. These findings suggest that selection bias may exist which may affect generalisability of primary-care based study results to all treated patients, thus there is a need for surveillance in secondary care.

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Utilisation of a once weekly injection for Type 2 Diabetes Mellitus: Interim results from an observational cohort study in England

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Background: Bydureon® (exenatide) is indicated for the treatment (Rx) of Type 2 Diabetes Mellitus (T2DM) in combination with metformin, sulphonylurea (SU), thiazolidindione (TZD) alone, metformin and SU or metformin and TZD for patients (pts) who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies alone. A post-marketing observational cohort study of Bydureon® was requested as part of the EU Risk Management Plan. The final target cohort size is 5000 pts. This study is ongoing.

Aim: To describe the utilisation characteristics of pts prescribed Bydureon® at interim.

Methods: An observational, population-based cohort design in primary care. Pts in the interim cohort were identified from all dispensed prescriptions for Bydureon® in England Sept 11–Jan 14 (interim data lock). Data were collected from prescribers via postal questionnaires sent ≥12mths after the 1st prescription was dispensed. Summary descriptive statistics were calculated.

Results: Evaluable cohort at interim = 520 pts; median age 58 years (IQR 51–65); 58.1 % male. T2DM and time since diagnosis was specified for 493 pts; the majority were diagnosed >10 years prior to starting Rx (210, 42.6 %). Where specified (n = 441), 91.1 % pts were classed as obese (BMI >30.0 kg/m2) immediately prior to Rx. On starting, 48.4 % (134/277) had a HbA1c >9 %, representing very poor diabetes control. Most pts had HbA1c ≥7.5 % (223, 80.5 %). The majority of pts used 2 mg once weekly (489/492, 99.4 %) and most pts were prescribed Bydureon® as either second line (158/477, 33.1 %) or third line co-therapy (307, 64.4 %). The majority of pts were prescribed Bydureon® with metformin (417/520, 80.2 %). Co-prescribing of insulin was also reported (117, 22.5 %).

Conclusion: These interim results characterise the utilisation of Bydureon® in primary care in England. The majority of pts had T2DM, used 2 mg once weekly and were co-prescribed metformin. Most pts were obese which raises the possibility of channelling by prescribers due to the purported benefits of Bydureon® in weight loss. This interim analysis will be superseded when validation and follow-up are complete for the final analysis.

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Utilisation and Safety of Deferasirox (Exjade®): Results from an Observational Cohort Study in England

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Background: Deferasirox is an oral iron chelating agent (ICA) primarily used to reduce chronic iron overload in patients (pts) receiving blood transfusions for various chronic anaemias and some non-transfusion dependant anaemias. Use in patients 2 years+ is licensed for certain indications. An identified safety concern is increased serum creatinine (Cr) during treatment (Rx); monitoring is therefore recommended prior to and during Rx.

Aim: To examine the utilisation and safety of deferasirox used in general practice in England.

Methods: Single exposure observational cohort study. Pts identified from dispensed prescriptions for deferasirox. Prescriptions collected Sep 06–Sep 14. Outcome data collected via postal questionnaires sent to prescribers ≥6mths after 1st dispensed prescription, including information on prior Cr measurements and prior use of alternative ICAs. Summary descriptive statistics calculated.

Results: Evaluable cohort = 122 pts (2–17 years = 51, 41.8 %); Median age = 23 years (IQR11-61); 58.2 % male. Frequent reasons for prescribing (underlying conditions leading to iron overload): sickle cell anaemia (27/103 where specified, 26.2 %) and beta thalassaemia (BT) (26, 25.2 %); 53.8 % BT pts had frequent blood transfusions (≥7 ml/kg/mth packed red blood cells). Most pts (43/51, 84.3 %) were prescribed licensed doses of 10 or 20 mg/kg/day at start. Rx initiated by a specialist for 100 pts (100/103, 97.1 %). 18 serum Cr values reported prior to Rx; 4 in excess of reference range [median value of all prior serum Cr 69 μmol/L (IQR51–95)]. Events reported in these 4 pts included raised ferritin and renal function decline. In total, 91 incident events were reported, including 2 raised serum Cr after starting Rx. 45.6 % pts (26/57) used an alternative ICA in the 12 months prior to Rx; 80.8 % desferrioxamine.

Conclusions: These results show that deferasirox is largely being prescribed for its licensed indications in general practice in England and events reported were consistent with the known safety profile. These results contribute to post-marketing information. However, considering

the small cohort size, any conclusions from this study should be put into context with results from other studies.

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The Ribavirin Pregnancy Registry: An Interim Analysis at the Mid-Point of Enrollment

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Introduction: Ribavirin, with interferons and/or direct acting anti-virals, is used to treat chronic hepatitis C. Significant teratogenic effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin has been contraindicated in women who are pregnant and in the male partners of women who are pregnant (1, 2). Both are advised to avoid pregnancy for 6 months after exposure. The Ribavirin Pregnancy Registry was established in 2003 to monitor pregnancy exposures to ribavirin in the United States to detect signals of possible human teratogenicity.

Aim: To evaluate interim findings from the Registry at the enrolment midpoint.

Methods: This voluntary registry aims to enrol 158 live births from pregnant women who were directly exposed, and 158 live births from those who were indirectly exposed during pregnancy or during the 6 months prior to conception. Exposure is classified as direct, women taking ribavirin, or indirect, women exposed through sexual contact, prior to or during pregnancy, with a man who is taking or has taken ribavirin in the past 6 months. Women are followed until delivery and infants for 1 year. The birth defect rate is calculated by dividing the number of live or stillborn infants (>20 gestation weeks) with defects plus the number of elective abortions with defects by the number of live births within each exposure category. Using available data, . preliminary rates were calculated. When sample size goals are met, the rates will be compared with the Metropolitan Atlanta Congenital Defects Program's published rate of 2.67 % (3).

Results: The Registry has enrolled 263 pregnant women with 171 live births: 7 birth defects cases among 80 directly exposed [7/80 (8.8 %) (95 % CI: 3.6, 17.2)], and 4 birth defect cases among 91 indirectly exposed [4/91 (4.4 %) (95 % CI: 1.2, 10.9)]. Of the 11 infants, 9 had structural defects and 2 had chromosomal anomalies. Patterns suggestive of a common etiology are not seen.

Conclusion: The Registry has reached only 54 % of its enrolment goal after 11 years. The current sample size is insufficient for reaching conclusions. Health care providers are encouraged to report all eligible pregnancies (http://ribavirinpregnancyregistry.com/).

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The New Definition of an Adverse Drug Reaction (ADR) with Focus on Abuse/Misuse: The Example of Pregabalin

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Introduction: The pharmacovigilance legislation, which came into force in 2012 introduced an amendment to the definition of an Adverse Drug Reaction (ADR). This is to include noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from uses outside the terms of the marketing authorisation thus now requiring explicitly the reporting of ADRs resulting from the misuse and abuse of a medicinal product, as well as from medication errors, overdose and occupational exposure. To our knowledge there are currently no studies conducted to assess data on abuse/misuse of medicinal products in the context of the EU pharmacovigilance.

Aim: To analyse EudraVigilance (EV) data and safety signals at the European Medicines Agency (EMA) related to abuse/misuse of medicinal products.

Methods: Analysis of data held in the EV database to show overall trend in reporting of abuse/misuse as well as changes after the implementation of the 2012 pharmacovigilance legislation. The reporting of abuse/misuse is discussed in the context of MedDRA coded data. Pregabalin is used as a practical example of a safety signal on abuse/misuse.

Results: The number of cases related to abuse/misuse has been progressively increasing and constitutes approximately 2 % of all cases reported to EV since 2005. Cases associated with pregabalin abuse/misuse amount for approximately 0.3 % of cases related to abuse of all medicinal products reported in EV. A nearly 2-fold increase in pregabalin abuse/misuse cases after 2012 was noted. Adverse drug reactions reported in the context of abuse/misuse in EV are an important data source for the early detection of a safety issue.

Conclusions: Broadening the definition of ADR is a significant step forward in monitoring the use of medicinal products outside the terms of the marketing authorisation and facilitating the detection of potential safety issues based on extended data sets in pharmacovigilance databases such as EV and targeted exchange of information with other EU authorities such as The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

Further sources of information/References

1. Directive 2001/83/EC as amended.
2. Regulation (EC) 726/2004 as amended.
3. MedDRA® Term Selection: Points to consider ICH-Endorsed Guide for MedDRA Users.

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Pregnancy Medication Error: Case Report

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Introduction: Fœtal heart failure and respiratory distress are well descripted in case of taking of NSAIDs during the last six or eight week of pregnancy [1]. Even if it is an adverse event well known, the junior doctor can made error and give this prescription to pregnant women. We present one medication error case in pregnancy received in Centre anti Poison et de Pharmacovigilance of Morocco (CAPM).

Case report: The CAPM received the case of newborn who was hospitalised during one month for heart failure and respiratory distress. The mother, Ms. AF 37-years-old, had been taken one dose of Voltaren ® (diclofenac) 75 mg/3 ml to treat migraine attack during the 36 week of pregnancy. 24 h later the diagnosis of fetal distress with abnormal heart rhythm was established and emergency extraction was performed. The outcome was favourable after one hospitalisation. The treatment was prescribed by junior doctor during the duty.

The CAPM performed the root cause analysis to detect the cause of error occurrence and to put in place the risk minimisation action to avoid the similar cases.

Discussion: Medication errors are very common during the night duty especially by junior doctors [2].

The CAPM was analysed the case received following pharmacovigilance process, the causality assessment was probable, and the case was preventable according to the P Method.

It was a pregnancy medication error with harm of newborn.

The root cause analysis has shown that the case was due to a lack of training of junior doctor and the lack of time to perform a good questionary with patients.

The CAPM has set up an action plan for training of junior doctor in hospital sitting concerning drugs fetotoxicity and sensitization session of pregnant women were organized to promote the rational use of drug during pregnancy.

Conclusion: Pharmacovigilance centres, have an important role in improving drug prescription and rational use of drugs during pregnancy and breastfeeding.

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Antituberculosis Drugs Induced Hepatotoxicity: A Retrospective Study In The Moroccan Pharmacovigilance Database

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Introduction: Hepatic injuries are more common adverse drug reaction (ADRs) induced by the first line antituberculosis drugs. They can compromise the effectiveness of the treatment and lead to severe complications that increase morbidity and mortality [1, 2].

Aim: To describe epidemiological characteristics of hepatic injuries induced by the first line antituberculosis drugs reported in Moroccan pharmacovigilance database.

Methods: We conducted a retrospective study of hepatic adverse reactions related to antituberculosis drugs between 2004 and 2014. All reactions related to Liver and biliary system disorders reported in the Moroccan pharmacovigilance data base were analysed. Causality assessment was performed by using the WHO method.

Results: Among 689 hepatic individual case safety reports collected between 2004 and 2014, 420 (60.96 %) were induced by antituberculosis drugs. The mean age of patient was 43.67 ± 18.38 years. Adults are mostly represented (85.7 %) and the women are more concerned (sex ratio = 0.68). 37.86 % of patients experienced at least two adverse reactions. The most common ADRs described according to preferred term classification were hepatic enzyme increased (42.8 %), hepatitis (17.7 %) and jaundice (11.2 %). Isoniazid and Rifampicin were included in all therapeutic regimens followed by Pyrazinamid (64.3 %), Ethambutol (45.5 %) and Streptomycin (4.3 %). The causality assessment according to the WHO method revealed that the relationship was scored in 57.5 % as "possible", in 38.1 % as probable, in 0.8 % as "certain" and in 3.6 % as "improbable" or without relationship. 56.9 % of the patients have serious ADRs. The outcome was favourable in 64.7 %.

Conclusion: Isoniazid, Rifampicin and Pyrazinamid have the most common hepatotoxic potential and their combination increases considerably the risk of hepatotoxicity induced by antituberculosis therapy. Knowing that most Moroccan are slow acetylators for NAT 2 gene and homozygous for c1 allele CYP2E1 gene [3] they are most prone to develop hepatotoxicity to anti-tuberculosis drugs. This genetic status should be considered in determining the minimum dose of Isoniazid to treat safely the tuberculosis patients.

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Antibiotic Resistance: What is the Sin Morocco?

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Introduction: In Morocco, despite the importance of the topic, no studies concerning the magnitude of the problem of bacterial resistance to antibiotics have been conducted nationally.
Aim: objective of the study is to make an inventory of the extent of this problem in our country.
Method: This work was based on the results of the various studies which have been performed in different cities of the kingdom
Results: In hospitals, the results of some studies have shown that the use of amoxicillin alone or in combination with clavulanic acid for the treatment of urinary tract infections, has recorded a resistance rate of E. Coli from 50 to 70 %. In the city, the growth of antibiotic resistance of this germ in community infections is also considered as a disturbing phenomenon since resistance rates remain very high.
There are many reasons for this resistance but the major determinant is the excessive and/or inappropriate use of antibiotics. Studies have shown that antibiotics represent more than 25 % of the total drug consumption in Moroccan hospitals. In addition, in our cities, there is also an abuse in the prescription of antibiotics. Their sale in pharmacies without medical prescriptions or diagnosis may explain the misuse of these drugs and the increase of self-medication. These bad habits in prescribing and increasing antibiotic consumption cause the change of the resistance patterns of bacterial species and the emergence of multidrug-resistant bacteria.
Conclusion: It is the time that all concerned institutions realize the seriousness of this problem. Strategy monitoring and management of this bacterial resistance should be adopted.
Key words: Bacteria-Antibiotics-Resistance

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Safety of Anticoagulants in Elective Hip and Knee Replacement Surgery: Pro-Change Cohort Study

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Introduction: Venous thromboembolism (VTE) is a potentially severe complication of major orthopaedic surgery. In 2011 the Italian Society of Orthopaedics and Traumatology published a guideline recommending the prophylaxis regimens .The approval of new oral anticoagulants offered an additional option; however, doubts were raised on the level of evidence for patients presenting risk factors that in clinical trials are considered as exclusion criteria.
Aim: To estimate the incidence of VTE and clinically relevant bleedings in patients receiving prophylaxis after hip and knee replacement and to investigate the role of risk factors (including the type of anticoagulant prophylaxis).
Methods: Multicenter observational cohort study of patients aged ≥18 years undergoing hip and knee replacement in four Italian hospitals between November 2013 and July 2015. Data were collected and recorded in a web-based archive at baseline and at 30 and 90 days after the procedure. The outcomes of interest were VTEs and clinically relevant bleedings occurring during the hospitalization and within the 90 days of follow-up. The effect of different risk factors on the occurrence of the study outcomes was assessed using a multivariate logistic model.
Results: The results currently available refer to the period 24 November 2013–27 April 2015; 639 patients were included (57 % hip and 43 % knee replacement). The median age was 71 years (70 and 73 years for hip and knee replacement, respectively) and 64 % were females. Almost all patients (94 %) were treated with enoxaparin; new oral anticoagulants were mainly used in two of the four hospitals. A total of 60 outcomes were observed: 53 (8.3 %) during the hospitalization and 7 (1.7 %) in the 30 days follow-up. The 90 days follow-up is still to be completed. Gender, smoking habits and chronic diseases were significantly associated with the occurrence of any events in the multivariate logistic model.
Conclusions: We estimated the association between different risk factors and the occurrence of thromboembolism and haemorrhagic complications in patients in routine clinical practice. Given the limited use of new oral anticoagulants in the study hospitals it was not possible to provide valid estimates of the effect of these drugs on the occurrence of the observed events. The proportion of bleeding events observed in our study is larger than those of the available literature, suggesting the need for continuous monitoring of drug safety in this area.

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Drug Commission of the German Medical Association—How to Make Use of Expert Knowledge for the National pharmacovigilance System

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Introduction: In Germany, physicians are requested by their professional code of conduct to report adverse drug reactions (ADR) to the DCGMA. The DCGMA is a committee for drug-related matters of the German Medical Association (GMA). Approximately 140 members, mainly medical specialists from all areas of clinical medicine, serve on this commission. The DCGMA participates in the National spontaneous reporting system since the late 1950's and cooperates with the two National competent authorities (NCA: Federal Institute for Drugs and Medical Devices, BfArM, and Paul-Ehrlich-Institute, PEI) on a contractual basis.
Incoming ADR reports are assessed first by medical specialists working in the DCGMA's central office. Cases are discussed at weekly meetings of the pharmacovigilance staff. In complex cases, one or more committee members are asked to assess the case and to give recommendations on measures to be taken. A subcommittee on adverse drug reactions, meeting twice a year, is the pharmacovigilance forum of the DCMA. The subcommittee consists of DCGMA members with special expertise in pharmacovigilance. Invited guests are representatives of the NCAs, a representative of the drug commission of pharmacists and a representative of the German poison information centers. The subcommittee decides on further steps to be taken e.g. publication of the case in the Medical Journal of GMA or the Journal of the DCGMA. With the representatives of the

NCAs, it is discussed whether regulatory measures would be appropriate to reduce the risk.
The DCGMA notifies German physicians and the public about results of its assessments and other drug safety issues by an email service called Drug Safety Mail in addition to the publications in the two Journals.
Aim: To illustrate the role of the DCGMA in the German pharmacovigilance system.
Methods: Data of pharmacovigilance activities from the ADR database, the archive and the website of the DCGMA from 2010 to 2014 were investigated.
Results: About 14.100 ADR reports were submitted to the DCGMA from 2010 to 2014. 206 case reports were assessed by clinical experts and 78 were discussed in the subcommittee. Thirty-five safety announcements were published and 259 Drug Safety Mails were sent out.
Conclusion: The concept of the DCGMA to involve physicians and their clinical experience to drug safety issues may serve as an efficient model for other countries as well.

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Health Care Professional Perspectives on Adverse Event Reporting by Treatment Setting in the United States: Underreporting and Educational Gap Insights

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Introduction: The underreporting of adverse drug events (ADEs) is an international health concern across the majority of regulatory bodies. Several studies have been conducted to assess the root causes underlying underreporting. However, few studies have focused on the United States.
Aim: To identify causes for underreporting AEs in US hospitals and ambulatory settings.
Methods: Tufts CSDD conducted a survey assessing the process for reporting ADEs in hospital, ambulatory, and retail pharmacy settings. Survey respondents were asked about: their experiences reporting ADEs; the process for reporting AEs at their primary treatment setting; and their thoughts on the causes for not reporting ADEs. The survey was conducted from May 16, 2014 to August 21, 2014.
Results: A total of 123 individuals completing the survey. 52 % and 51 % of respondents noted that uncertainty about reporting procedures and whom to report to is often the cause for preventing health care professionals from reporting ADEs respectively, while 39 % of respondents noted that they are unaware of the benefits of reporting. 20 % and 10 % of respondents indicated that ADE reporting can be improved with more awareness and training, educating the public on how to report events.
Conclusions: This study has identified factors that contribute to the underreporting of adverse drug events in the United States. The lack of education within both hospital and ambulatory settings is a noteworthy factor. A suggestion therefore is to provide treatment setting-based continuing education and training to all stakeholders in order to increase awareness of the importance of reporting events and processes that should be followed in each setting to report

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Analysis of Adverse Drug Reactions of Medicines, Used in Assisted Reproduction Techniques, Extracted From Publications in Social Media in Bulgaria

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Introduction: Patients are direct participants in the spontaneous reporting of adverse drug reactions (ADRs) in Bulgaria since 2012. However the rate of ADRs reported by patients to the competent authorities is still low. On the background of the significant under-reporting of AEs through official channels, new medically orientated internet forums have given voice to patients who share information about their therapy, including experiences with adverse events. As a result some vital risks are being discussed online.
Aim: To compare ADRs of medicines, used in Assisted Reproduction Techniques (ART), identified in consumer reviews from online forums and the corresponding data, mentioned in the SPC and the data, collected from the Bulgarian Drug Agency reporting system.
Methods: Both Google and selected medical web-based forums search was conducted using the following key words in Bulgarian: Adverse drug reaction, side effects, assisted reproduction, in vitro fertilization (IVF), ovarian stimulation. In addition a search for the INN and the trade names of medicines from the focus group was performed-Corfollitropin, Follitropin alfa, Follitropin beta, Urofollitropin, Menotropin, human menopausal gonadotropine. A systematic review of the SPCs of the medicines, approved by the Bulgarian Drug Agency, current to the date of the consumers' web posts.
Results: The study identified 200 reports with resemblance to adverse events, among a sample of 1000 posts collected from 25 specialized forums, posted between November 2013 and May 2015. In comparison, there is no adverse events reported to The BDA for the same period. Forum discussions, used for extracting the consumer reviews are locked for changes and/or deletion by moderators. The most often complaints, shared by women are pain in the waist, weight gain, retention of fluids, syndrome of ovarian hyper stimulation, emotional disorders, as a result of

stimulation hormones application. Most of the adverse effects, posted in the internet publications are mentioned in the SPCs, except for specific rheumatoid-like pain in hands and fingers, following injection of Follitropin beta; faintness and drowsiness as a result of menopausal urine gonadotropins; an isolated case of myoma after injection of Urofollitropin.
Conclusion: The rate of reporting of ADRs by the official pharmacovigilance channels is still extremely low, especially for hormones, used for ovarian stimulation during fertility therapies. At the same time internet forums and chat rooms can be a source of valuable first-hand information for disorders, resulting from application of hormones mentioned above.

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Safety Assessment of Food Additives in Top-selling Dietary Supplements in the Czech Republic

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Introduction: Food additives find use not only in the food industry but also in the pharmaceutical sector. They are present mainly in medicines on which CZK70 billion a year are spent on average and in dietary supplements (with CZK5.5 billion a year spent) [1]. Food additives should be safe if the acceptable daily intake is complied with; however, some individuals can experience immediate effects such as headache or impaired mental concentration, behaviour, and immune response. Long-term effects may increase cancer or cardiovascular disease risk in some individuals [2].
Aim: To evaluate the frequency of potentially harmful excipients in the bestselling dietary supplements in the Czech Republic and to consider their adverse effects.
Methods: From the list of the bestselling dietary supplements (DS) in the Czech Republic in 2014, their active ingredients and excipients were identified using the database of the information system Decisions of the Chief Public Health Officer (IS RoHy). The IS RoHy collects data on any DS registered in the Czech Republic. Adverse effects of the excipients were retrieved from the PubMed and Medline databases and from the websites of the European Safety Authorities, Joint FAO/WHO Expert Committee on Food Additives, and Codex Alimentarius.
Results: In total, 418 DS were identified, including 229 DS for children under 12 years of age. Of these, 51.9 % contained at least one additive known to have a negative health effect. On average, there were five additives per DS. The most frequently reported additives were glycerol (28.6 %) sorbitol (12.9 %), lecithin (10.5 %), beeswax (5.7 %), and sucralose (5.2 %). The most commonly found potential adverse effects caused by additives as reported in the literature were gastrointestinal symptoms (49.5 %), hypersensitivity reactions (31.3 %), or attention-deficit/hyperactivity disorder (6.5 %).
Conclusions: An EU list of approved and therefore safe additives has been established [3]. Nevertheless, half of the most commonly used DS contained additives known to have adverse health effects. Such effects may potentially occur in predisposed patients and vulnerable groups of the population such as children or chronically ill patients, especially in the case of intake of multiple products containing the same additive. Further studies are needed to assess the clinical impact of adverse effects in DS users.

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Patient-Generated Data and Digital Engagement—Social Media: Its Impact and Contribution to Pharmacovigilance

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Introduction: Patient adverse event reports (PAER) reports have been shown to positively contribute to the ongoing benefit: risk versus assessment of medicines. In response to the rapid expansion of social media, PAER from web-based sources have the potential to be exploited as alternative sources that may, if extracted and analysed appropriately, provide complementary data to that obtained from routine pharmacovigilance (PV) activities.
Aim: To collect and assess the attitudes of PV professionals regarding the utilisation of safety data from social media for PV purposes.
Methods: A cross-sectional survey was conducted between August to September 2014 inclusive using web-based tool (Survey Monkey™) using a format of open/closed and Likert scale based questions, to gather anonymous information at an international level of PV professional characteristics (profession, work place and PV experience) and opinions on the value, quality, benefits and challenges of utilising PAER data obtained via social media. For PV professionals working in pharmaceutical industry (pharma), information was also requested on operational activities such as how such data were being gathered. The University of Portsmouth Science Faculty Ethics Committee (ref 17/7/14) provided study approval. Eligible participants comprised 5329 PV professionals from pharma, regulator and academic backgrounds registered on a mailing contact database. Data confidentiality was assured by the survey being managed by the database manager independent of the investigators. Data analysis comprised qualitative thematic evaluation and quantitative descriptive statistics.
Results: 197 participants (3.7 % eligible) responded from a wide range of professional backgrounds-the most frequent being from academia (n = 44, 22.3 % responders), from pharmaceutical industry sector (n = 143, 72.6 %), and with less than 10 years experience (n = 118, 59.8 % responders). Where specified, 74.8 % (107/143) believed PAER data obtained via the internet have the potential to contribute valuable

information to the benefits and risks of medicines in a real-world context; 68.2 % (118/173) agreed that such data provided an opportunity to increase the amount of safety data and also specifically inform on how adverse events affect quality of life. Concerns included data quality, burden on resourcing and relevant guidance. Of 112 PV pharma professionals, 34 (30.4 %) reported awareness of their company engaging in activities such as searching non-company sponsored websites (digital 'listening').

Conclusions: Internet derived patient-generated data clearly has the potential to contribute to ongoing risk versus benefit assessment of medicines. However a number of issues still need addressing. Continual improvement of methodological techniques is required with relevant regulatory driven guidance with regards to PAER signal detection purposes.

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Antiretroviral Treatment Change Study at the Regional Referral Center for Care of PLHIV of Agadir in Morocco

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Objective: To estimate the rate of combination antiretroviral treatment change also to identify and analyse the causes of change.

Methods: It is a retrospective study from 1 January to 31 December 2014.the analyses were based on patients on antiretroviral treatment followed at the regional referral centre who undergone a change in treatment. The database was made from registers of therapeutic mediation, medication management software (ODE) and Patient records.

Results: At the end of this study, 65 patients including 36 women and 29 men with an average age of 38.6 ± 9.36. The scheme including 2 INTI + 1 INNTI was the mostly used (86.7 %). Association (Zidovudine + Lamivudine) associated with Efavirenz was the mostly represented (36.2 %). Most of patients have undergone only one change (98.2 %). Among the molecules in cause of substitution, association of Efavirenz and Zidovudine has been the mostly represented respectively (35.3 and 27.8). Side effects and therapeutic failure have been the most significant reasons of change (48 and 43 %). In 14 % cases the scheme has been completely replaced due to stock shortage.

Conclusion: In this study, we find that the side effects associated with the use of ART is the leading cause of treatment change. To this end, an EMC study remains necessary to improve patient safety on the use of antiretroviral drugs and to evaluate the incidence of serious adverse effects of ARV.

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Metabolic Side Effects Following the Use of Anti-TB Drugs in Morocco

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Introduction: The TB metabolic side effects are rare but can cause serious problems for TB patients if they are not well known.

The objective of this study was to estimate the frequency, type, severity, evolution and incriminated medication of these effects.

Materials and methods: A prospective study was performed during 3 years (2012-2014). After several awareness sessions of pharmacovigilance in favour of Moroccan phthisiologists, they have notified all TB adverse events (AEs) through a notification system. Each notified AE is studied by a pharmacologist of Moroccan pharmacovigilance centre and a detailed response is sent to the phthisiologist network. All reported cases are recorded in Moroccan database and systematically sent to VigiFlow.

Results: During this period 11 metabolic AEs were reported. Their average age was 41.3 ± 17.3 years [24, 72], sex ratio was 1.5. There were 4 MDR TB, 6 pulmonary TB and one unknown TB. 5 cases of hypoglycemia (0.6 %), 5 cases of hyperuricemia (0.6 %) and one case of hyperkalemia (0.1 %) were reported. Hypoglycemia occurred with the first and second-line drugs, hyperuricemia occurred only with first-line drugs and hyperkalemia occurred only with second-line drugs. Two serious cases occured: hypoglycemia and hyperuricemia associated with mixed hepatitis. The outcome was favourable in all cases following adequate monitoring and symptomatic treatments.

Conclusion: The TB metabolic side effects are rare but require special pharmacovigilance especially in hyperkalemia that expose to a major heart risks.

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Pharmacovigilance System Implementation in a Middle-Income Country: the Case of the Dominican Republic

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Introduction: Pharmacovigilance development remains heterogeneous in Latin America. In 2014, nearly half of the countries (9/22) were still not enrolled in the WHO Program for International Drug Monitoring. The implementation of pharmacovigilance systems in these countries is necessary and remains a challenge. Pharmacovigilance is anticipated by Dominican Republic legislation and should be led by the Ministry of Health. However, limited actions have been taken so far.

Aim: To develop the bases of a pharmacovigilance system in the Dominican Republic.

Methods: In 2013, a pilot study was conducted in a semi-public hospital in Santo Domingo, Dominican Republic. The program included passive and active collection of adverse effects (AEs), followed by an assessment

according to Naranjo algorithm and codification according to ATC classification, WHO–ART, and ICD-10. Reporting and codification forms were specially designed in paper and electronic format. A database tailored to the program requirements was set up. Staff training sessions were performed to ensure the program's maintenance. Several meetings were held to raise awareness regarding spontaneous reporting among healthcare staff including physicians, nurses, pharmacists and medical residents. In addition, several lectures were held at the Universidad Autonoma de Santo Domingo, among several institutions. Project follow-up meetings were organized with the Dominican Republic Ministry of Health.

Results: This pharmacovigilance program is currently functional with 177 case reports over 21 months. In 2014, an average of seven notifications per month has been observed following 150,000 visits (including outpatient consultations). Spontaneous reports represented 30 % of the total and this proportion is increasing. The program produced exploitable results and conducted to changes in hospital therapeutic protocols. Unfortunately, due to financial resource constraints, codification according to WHO–ART was not possible. Protocol and forms adapted to a national level use were given to the Dominican Republic Health Ministry.

Conclusions: This experience has showed that the implementation of a pharmacovigilance system in a middle-income country is possible. In order to overcome the current limitations of this program, such as lack of resources, tangible supports from local or international authorities as well as more adequate and specific healthcare training are required. Nevertheless, this program showed its efficacy and would merit to be extended to other pilot hospitals. To date, the Dominican Republic Health Ministry has the means to implement such a program. However, political will is needed to support such a project.

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Assessing the Feasibility and Performance of the HAWK Electronic Medical Records for Drug Safety Surveillance

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Introduction: The Healthcare research Application for real World Knowledge (HAWK) is a new database that consists of electronic medical records (EMRs) of a network of general practitioners from the province of Ontario (Canada). Its usefulness for drug safety surveillance has not yet been examined. Elsewhere, EMRs are increasingly used for drug safety surveillance as they provide information not included in spontaneous reporting databases. The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) is a standardized analytical tool specific to drug safety surveillance using longitudinal data such as EMRs. To our knowledge, this tool has not yet been applied in a Canadian healthcare database.

Aim: To assess the feasibility and performance of the HAWK database for active drug safety surveillance using OMOP CDM.

Methods: Using the OMOP CDM version 4.0, the project consisted of three phases: (1) Development of a CDM infrastructure; (2) Data characterization and quality control; (3) Disproportionality analysis. An extraction, transformation and loading process was applied to a sample of 30,000 patients identified in the HAWK database. Mapping and transformation of Canadian Drug Identification Number (DIN) into RxNorm codes, as well as from ICD-9 diagnostic codes into SNOMED-CT were conducted. The OMOP Observational Source Characteristics Analysis Report (OSCAR) was used to summarize CDM healthcare data and produce descriptive statistics. HAWK CDM specific outputs will be compared with other OSCAR outputs obtained in other databases to check for consistency. In phase 3, disproportionality analysis will be conducted using known drug-event associations using Bayesian Confidence Propagation Neural Network.

Results: Overall, 86 % of drug DIN codes could be mapped to RxNorm codes directly. Of the ICD-9 diagnosis codes, 83.4 % were mapped to the SNOMED-CT dictionary. The 11 remaining unmapped diagnoses were manually reviewed to achieve the highest mapping level. The top 100 drugs and top 100 diagnoses mapping in the HAWK CDM were manually coded achieving around 96 % of mapping. These represent respectively 47.5 and 90.1 % of the automatized mapped drug data, and of the automatized mapped condition. OSCAR results and disproportionality analyses will be generated and presented.

Conclusions: Preliminary results indicate that the HAWK database can be reliably transformed into OMOP CDM with few unmapped codes across drugs and conditions. These initial results suggest that the HAWK CDM will be a unique database in Canada for the conduct of disproportionality analysis for the purpose of signal detection using the OMOP ecosystem.

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Estimation of Theoretical Cost Preventability Achievable with an Effective Pharmacovigilance Activity in a Pharmacovigilance Regional Centre in Italy

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Introduction: The management of patients with adverse drug events (ADEs) has a significant economic impact owing to hospitalization and treatment costs. Recently, social and healthcare costs related to ADEs have become a relevant issue, and they are increasingly being included in budget estimations for health resource allocations.

Aim: To evaluate the costs of ADEs and their predictability, and to estimate the impact of a pharmacovigilance facility on ADE-related cost savings within a regional healthcare system.

Methods: A systematic review of English medical literature quoted in PUBMED (January 2005–March 2015) was conducted. We included all studies performed in Western Europe, USA and Canada about direct costs of ADEs in inpatient settings, for which the mean cost of serious and/or not-serious ADEs could be estimated. Studies on specific side-effects or drug-classes were excluded. The following data were extracted: mean cost of ADEs; percentage of preventable ADEs; charges for outpatient care and medications. The mean cost (into Euros) of serious and not-serious ADEs and the mean percentage of preventable ADEs were estimated. Based on

spontaneous ADE reports recorded by the Tuscan Pharmacovigilance Centre in 2014, the theoretical cost of ADEs in Tuscany (3,704,152 inhabitants) was calculated. A sensitivity analysis was performed about cost (mean cost ±standard deviation ±50 %), and preventability (the maximum and minimum percentage estimated). The resulting range of ADE costs and the theoretically costs-saving that can be achieved with the implementation of pharmacovigilance activities were assessed.

Results: Fourteen studies were analyzed: 13 on serious ADEs; 3 on costs of not-serious ADEs; 8 on percentage of preventability. The mean cost of an ADE was: €3526 ± 1927 for serious and €172 ± 93 for not serious. We estimated a mean preventability of 51.3 ± 21 %. In 2014, the Italian National Network of Pharmacovigilance database accounted for 1498 serious ADEs and 2997 not-serious ADEs in Tuscany (1214 ADEs/million-inhabitants). The overall costs of ADEs incurred by the Tuscan Regional Healthcare System was: €5281,948 (€1,425,953/million-inhabitants; sensitivity analysis: €3304,827–322,957/million-inhabitants) for serious ADEs; €515,484 (€139,164/million-inhabitants; sensitivity analysis: €321,094–32,117/million-inhabitants) for not-serious ADEs. Based on the estimated preventable costs in Tuscany, an effective pharmacovigilance system could allow to save €2,974,083 (€802,905/million-inhabitants; sensitivity analysis: €1,697,370–237,115/million-inhabitants) over one-year.

Conclusion: Resource allocations to improve the regional pharmacovigilance systems might increase appropriateness and safety of therapies, thus reducing the costs incurred by regional healthcare systems. It could be obtained through: ADE evaluation systems; computerized prescription systems with alerts; continuing education of health professionals; multidisciplinary support to medical therapies.

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Bleeding Related to Oral Anticoagulant Drugs as Cause of Emergency Department Admission: Analysis of Data from the Tuscan MEREAFaPS Network

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Introduction: The introduction of novel oral anticoagulants (NOAs: dabigatran, rivaroxaban, apixaban) into clinical practice was expected to reduce the incidence of bleeding associated with traditional oral anticoagulants [1].

Aim: To assess the trend of the contribution of admissions to Emergency Department (ED) for adverse drug reactions (ADRs) attributable to bleeding in patients receiving oral anticoagulants after marketing authorization of NOAs.

Methods: The analysis was performed using data in Tuscany collected from January 2012 to December 2014, during MEREAFaPS, an observational study investigating drug-related admissions to EDs in Italy. Dabigatran, rivaroxaban and apixaban were introduced in Italy in 2008, 2009 and 2012, respectively, for prevention of venous thromboembolism; they were then approved for prevention of stroke and systemic embolism in non-valvular atrial fibrillation in 2013. In 2012 there were no reports of bleedings associated with NOAs. Cases were patients with a report of bleeding (MedDRA) associated with oral anticoagulants. The rate of overall and serious bleeding was weighed by the number of ADR reports and by the total number of admissions recorded in the Tuscan MEREAFaPS Network.

Results: The analysis included 1,017,034 ED admissions, of which 6254 were related to ADRs (0.61 %) and 443 (231 males and 212 females) were bleedings associated with oral anticoagulants (0.044 %). Among these, 186 cases were serious ADRs. The most frequently recorded serious bleeding ADRs included: melena (16.7 %); epistaxis (12.9 %); rectal bleeding (11.8 %); hematemesis (8.6 %); cerebral hemorrhage (8.6 %); hematuria (8.1 %). The prevalences of anticoagulants associated with bleeding-related admissions were: warfarin (92.1 %); acenocoumarol (1.8 %); dabigatran (4.1 %); rivaroxaban (2.0 %) and apixaban (0 %). The annual incidences rates of bleeding associated with anticoagulants were 27, 17 and 34 cases per 100 admissions due to any ADR per 1,000,000 admissions/year in 2012, 2013 and 2014, respectively. When only serious bleedings were considered, the incidence rates were 9, 7 and 16 cases of bleeding per 100 admissions due to any ADR per 1,000,000 admissions/year in 2012, 2013 and 2014, respectively.

Conclusion: Our preliminary analysis suggests that the introduction of NOA into the clinical practice has not reduced the proportion of ADRs attributable to anticoagulant-related bleeding among the overall ADRs that cause drug-related admission to ED. In this setting, the use of NOAs is likely too limited to account for a reduction of this trend.

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Use and Toxicities of Linezolid as Used in Severely-Ill Patients in Two Teaching Hospitals: A Retrospective Study

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Introduction: Linezolid, active against Gram-positive organisms resistant to other antibiotics, has a restricted use in Belgium (hospital delivery only) because of concerns about resistance emergence, toxicities upon prolonged treatments, and cost. The current Summary of Product Characteristics (SmPC) states that linezolid is only indicated for (1) nosocomial and community acquired pneumonia and (2) complicated skin and skin structure structures infections, with a maximal duration of treatment of 28 days.

Aim: To assess the linezolid actual uses and attributable toxicities as currently used in teaching hospitals, knowing that it is often prescribed off-label and for longer durations than provided for in the SmPC.
Methods: Patients having received linezolid over 1 year period in 2 academic hospitals were identified using Pharmacy records. Medical files were analysed for indication, reason for prescribing linezolid, duration of treatment, routes of administration, side effects and contra-indicated drugs administered to the patient (the two latter based on the corresponding listings of the SmPC).
Results: 39 medical files (40 treatments) could be retrieved. All treatments were curative with 37 being off-label (treatment of endocarditis, deep infected trauma, septicemia, catheter-related infection, tuberculosis …) but based on the isolation of a susceptible organism in all cases (linezolid replaced vancomycin in 24 cases because of resistance [n = 5], renal toxicity [n = 7] or difficulties in maintaining an IV line [n = 7]). Treatment durations varied from 2 to 92 days (median: 24; mean 33.1). Administration was IV, oral or sequential (IV followed by oral) in 9, 27 and 4 treatments, respectively. An untoward effect attributable or likely to be attributable to linezolid was observed in 9 and 22 cases, respectively (but reported by the attending physician in only 10 cases), with the most frequent and severe being (1) anemia (>20 % decreased of red blood cell counts in 10 patients); (2) thrombocytopenia (>50 and >20 % decrease of platelets in 13 and 26 patients, respectively [5 patients required transfusion(s)], without correlation with treatment duration; (3) lactic acidosis (3 cases but of uncertain origin). Drugs considered as contraindicated were administered in 29 patients with 15 being susceptible to cause a serotoninergic syndrome (not observed).
Conclusion: Linezolid is most often used off-label (but for good microbiological reasons) for longer periods than recommended and causes a large number of side effects (often not reported). Direct analysis of medical files could help in better assessing the true benefit/risk ratio of restricted drugs especially when used largely out of the registered indications.

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Effects on Blood of Clozapine in Patients under Schizophrenic Antipsychotic Therapy Incorporated in a Drug Surveillance Program in Venezuela

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Aim: Schizophrenia is a mental illness that causes a large disruption in social relationships, family and work. The 2 % of the general population suffers, ie seven in every thousand adults have a diagnosis of schizophrenia. Clozapine has proved a different antipsychotic involving conventional neuroleptics improvement in the quality of life of these patients, however, the main reason for discontinuing the use of clozapine is hematologic adverse effects, since these can even be fatal. Clozapine in Venezuela began selling in 1993, since which it has been following the diagnosis of patients with refractory schizophrenia. The aim of this study is to prove that with a good intensive pharmacovigilance programme we can achieve a good adherence to clozapine treatment.
Methods: We conducted a descriptive study of haematological adverse effects (leukopenia type) related to the administration of clozapine in schizophrenic patients refractory to conventional antipsychotic therapy, incorporated into an intensive pharmacovigilance program in Venezuela, from 1993 until 2014.
Results: Among the patients enrolled (4040), (1715) were women and the rest 42.45 % (2325) 57.55 % men. The number of patients with adverse effects such leucopenia and Alarm 1 was (442), followed by the Alarm 2 to (155), then the alarm (17) 3A and 3B after Alarm (9) patients, representing a rate of 0.23 the total. The proportion of cases of leukopenia was similar to that reported in the literature of clozapine.
Conclusion: We recommend to include this pharmacovigilance protocol information along with the medication and to alert patients that by following these guidelines the treatment could be safer.
Clue Words: Hematologic Side Effects, Clozapine, Schizophrenia, Pharmacovigilance, Alarms

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Children Adverse Drug Reactions in Emergency Department: An Analysis of MEREAFaPS Study National Database

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Introduction: Adverse drug reactions (ADRs) are an important cause of mortality and morbidity and have a significant impact on health care resources. In western countries, ADRs cause 3 % to 5 % of all hospital admissions and are responsible for about 5 % to 10 % of in-hospital costs. In paediatric patients the monitoring of drug use and of ADRs requires careful evaluation, since many drugs are used off-label, due to the lack of registrative studies in this age group.
Aim: Aim of the present study is to give a "real-life" information on safety profile of drugs used by paediatric patients, information that now is only based on data coming from clinical trials conducted on adult population.
Methods: We analysed the impact of ADRs on Emergency Department (ED) accesses, using data from a national pharmacovigilance project of ADRs monitoring in ED (Monitoraggio Epidemiologico di Reazioni ed Eventi Avversi da Farmaci in Pronto Soccorso-MEREAFaPS) and we focused our attention on children.
Results: This study considered ADR reports form patients with 18 year or less admitted to 94 Italian EDs for a suspected ADR from January 2010 to March 2015. The reports were stored in a structured Italian database called Niguarda database. ADRs were classified according to System Organ

Class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA) and were classified serious if they caused or prolonged hospitalization, were life-threatening, resulted in death, or produced permanent malformations or disabilities. In a period of five-years, the number of paediatric admissions to ED due to ADRs was 3839 representing 9 % of the total reports records in the MEREAFaPS study. Fifty-one percent of the reports involved female children with a mean age of 6 years (standard deviation 5.9 years). Serious reactions requiring hospitalization represented 14.5 % of total ADRs, only 8 being life-threatening; thus, the majority of ADRs were classified as 'not serious'. As expected, the reporters were mainly hospital doctors (62 %), followed by pharmacists (36 %) and other healthcare professionals including nurses. The 3839 ADR-related ED admissions resulted in 6006 adverse events: 42 % involved the skin, 15 % the gastrointestinal system, 15 % were related to general disorders and administration site conditions and 6 % to nervous system disorders. Drugs (n = 4761) most frequently involved in the ADRs were vaccines and antibacterials for systemic use.

Conclusions: Results from this study could help minimizing ADRs incidence in the paediatric population and increasing awareness about drug safety.

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Acute Epigastric Pain and Liver Toxicity Associated with Acetaminophen-Codeine Use in Cholecystectomized Patients

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Introduction: Acetaminophen-codeine (AC) fixed association represents the standard medication in the second step of the World Health Organization analgesic ladder and is the most commonly used opioid analgesic for a variety of pain conditions. Side effects of AC consisting of nausea, vomiting, and constipation, may be considered minor when compared to those of NSAIDs. Cholecystectomized patients may present disorders on gastrointestinal tract. In fact, these patients have a high predisposition to develop spasms of the sphincter of Oddi and have an increase of the surface area of Vater's Papilla. This variation may represent an obstruction to the normal biliary-pancreatic flow and the drugs excreted through the bile may remain for a longer time in the liver, especially in the bile duct. Morphine (codeine metabolite) has a biliary excretion.

Aim: To investigate the incidence of acute epigastric pain and the association between this side effect and AC use, from September 2012 to September 2013, we collected data on patients admitted to Prato Hospital Emergency Department (ED) and identified those admitted for acute epigastric pain and hepatic enzymes increase. To quantify the association we calculated Odds Ratios (ORs) and corresponding 95 % Confidence Intervals (CIs) using multivariable logistic regression models.

Results: During a period of one year, 76,761 patients were admitted to Prato ED and among them 2339 (3 %) were diagnosed with acute epigastric pain. OR for AC use was 3.57 (95 % CI: 2.64–4.82) compared to non-use. This association was higher in cholecystectomized patients (OR 11.38; 95 % CI: 5.06–25.62). In the majority of cases (64.7 %), we observed an increase of liver enzymes related to the onset of acute epigastric pain after AC administration.

Conclusions: Although in cholecistectomized patients use of AC is not strictly contraindicated, data from present research quantify the risk of acute epigastric pain and identify the liver toxicity in this population. We could assume that, if the results of this study were confirmed, the use of AC could be considered contraindicated in this specific population. However, further studies are necessary to confirm and extend results here reported.

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Ticagrelor-Related Dyspnea in Patients with Acute Coronary Syndrome: A Three Year Cohort Study

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Introduction: The occurrence of dyspnea in acute coronary syndrome (ACS) patients has always been considered a challenging diagnostic and therapeutic clinical scenario. In the last few years, the potential association between ACS and dyspnea has also become more challenging with the increasing use of ticagrelor in these patients due to drug's beneficial effects on ischaemic event prevention and mortality, since ticagrelor can induce dyspnea as adverse drug reaction (ADR).

Aim: In order to better understand the post-marketing incidence of ticagrelor-related dyspnea, as well as its implication on drug discontinuation, we conducted a retrospective cohort-study on all ACS subjects admitted to Florence Hospitals for dyspnea.

Methods: Between January 1, 2012 and December 31, 2014, 1174 consecutive patients treated with ticagrelor after an ACS were identified. Among these, for 1073 was possible collect data on hospital discharge records. Demographic records and drugs utilization were obtained from administrative archives of the Florence Local Health Authority. The occurrence of respiratory disorders or ticagrelor-related dyspnea was recorded.

Results: Among 1073 patients, 75.5 % were males with a mean age of 55 years (standard deviation 12.1 years). A total of 261 patients (24 %) had respiratory disorders. In the present study we observed that a high proportion of patients experienced respiratory disorders during ticagrelor administration. A high number of these events could be ticagrelor-related dyspnea.

Discussion: It has been hypothesized that the sensation of dyspnea in ticagrelor-treated patients is triggered by adenosine, because ticagrelor inhibits its clearance, thereby increasing its concentration in the circulation. We would like to emphasize the possibility of a "real world" underestimation and mismanagement of ticagrelor-related dyspnea also caused by the difficulty to fully ascertain its causality assessment, especially in ACS elderly patients treated with several drugs. Physicians should consider this potential association in daily clinical practice to reduce time of diagnosis.

Conclusions: In conclusion, in order to better manage ACS patients who present at ED with respiratory distress and no other cardio-respiratory and

metabolic conditions, it is necessary for prescribing healthcare professionals to consider ticagrelor replacement in order to maintain in ACS patients (1) antiplatelet therapy compliance and (2) a high quality of life without compromising their cardiovascular safety. Our study could be useful to identify the optimal strategy to manage ticagrelor-related dyspnea and its possible consequent replacement therapy.

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Comparison of Adverse Drug Reaction Imputation with Different Causality Algorithms

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Introduction: Different algorithms are available to standardize adverse drug reaction (ADR) causality assessments [1]. Although most algorithms refer to the Austin Bradford-Hill criteria for causality (ie. strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy), variation exists among the imputation results that depends on the algorithm applied to perform evaluation [2].
Aim: The study compared the results of ADR imputation obtained from different algorithms and identified the most suitable algorithm to carry out ADR causality assessment in a Brazilian public hospital.
Methods: A cross-sectional study was performed to assess the causality of ADR reported in a public hospital of São Paulo (Brazil). Four assessors independently assessed the causality of 44 ADR using 10 algorithms: Gallagher et al. [2011]; Edwards and Biriell [1994]; Venulet et al. [1986]; Emanuelli [1984]; Mashford [1984]; Jones [1982]; Naranjo et al. [1981]; Blanc et al. [1979]; Kramer et al. [1979]; Karch and Lasagna [1977]. Due to lack of consistency in imputation terminology between the instruments, equivalents terms were grouped as follows: definite, probable, possible, and improbable [2]. Imputation data were compared and analysed using the Kappa index of reliability.
Results: No algorithm showed 100 % agreement in ADR imputation. The assessors achieved fair inter-rater reliability with a global kappa of 0.27 (SD $\pm$ 0.07).Venulet ($k = 0.15$), Kramer ($k = 0.19$), and Naranjo ($k = 0.20$) all obtained slight agreement in ADR imputation. Emanueli ($k = 0.36$) and Edwards and Biriell ($k = 0.36$) were instruments with better scores.
Conclusions: The Edwards and Biriell (1994) algorithm may be the most suitable for ADR causality in a hospital setting, as it includes Austin Bradford-Hill criteria and allows qualitative evaluation of the reports. However, algorithms should include information regarding medication errors, quality deviations, and therapeutic failure due to noncompliance with pharmacotherapy or technical complaints of drugs in order to improve ADR causality assessment.
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Impact of Pharmacovigilance Multifaceted Educational Intervention on Knowledge, Skills and Attitudes of a Multidisciplinary Healthcare Team

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Introduction: Most educational interventions in pharmacovigilance are designed to motivate physicians to report adverse drug reactions (ADR) [1, 2]. However, multidisciplinary health teams may play an important role in alerting authorities about drug-related problems.
Aim: We assess the impact of a multifaceted educational intervention in pharmacovigilance on the knowledge, skills and attitudes of hospital health professionals.
Methods: We performed a longitudinal, non-randomized study in a general and public hospital of medium complexity with 104 beds in São Paulo, Brazil. We conducted educational intervention for 173 professionals on multidisciplinary health care teams via (1) presentation of a lecture about the landscape, importance and concepts related to pharmacovigilance; (2) classroom time to elucidate how to correctly fill out adverse drug event (ADE) reports; (3) distribution of educational manual and (4) the application of a questionnaire to assess knowledge, attitudes and skills in pharmacovigilance. The impact of intervention on knowledge and skills was assessed by comparison of answers of questionnaire with gold-standard parameters: minimum and desired criteria [3] to fill the ADE form and definitions of World Health Organization and Pan American Health Organization [4]. The impact on attitudes was evaluated by follow up of the prevalence of adverse drug events (ADE) reported in 12 months prior and before intervention. Mann-Whitney statistical test was applied to verify significant difference between both periods.
Results: Educational intervention was effective for acquisition of knowledge ($p < 0.0001$) and skills ($p < 0.0001$) in pharmacovigilance and increased the prevalence of ADE reports by 185-fold. Drug-related problems included medication errors ($n = 165$), ADR ($n = 26$), quality deviations ($n = 18$) and therapeutic failures ($n = 5$). Nursing staff reported the majority of cases ($n = 150$), followed by pharmacists ($n = 29$), physicians ($n = 6$) and physiotherapists ($n = 1$).
Conclusions: Multifaceted education intervention is effective at changing the behaviour of multidisciplinary teams to detect and alert suspicions ADE, as well as to aware them about drug safety. Therefore, the inclusion of all health professionals in post-market surveillance is an important strategy to decrease ADE underreporting and improve risks communication associated with drug use.
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Active Pharmacovigilance to Determine the Incidence and Severity of Adverse Reactions Associated with Anthracyclines-Based Chemotherapy in Cancer Paediatric Patients

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Introduction: Anthracyclines have been included in over 50 % of the protocols of cancer treatment in children. Although they have helped to increase the survival rate of patients with cancer, their use is limited by the presence of adverse reactions [1–2]. Cardiotoxicity is the best known reaction associated with anthracyclines, nevertheless there are another reactions associated that are impacting in quality life of the patient and treatment success [3]. In Mexico, there are no data of the incidence and severity of the adverse reactions associated with anthracyclines-based chemotherapy due to the low spontaneous reporting and lack of studies of pharmacovigilance in paediatric population.
Aim: To determine the incidence and severity of adverse reactions associated with anthracyclines-based chemotherapy in cancer paediatric patients.
Methods: A retrospective cohort study of children treated with anthracyclines-based chemotherapy in two paediatric hospitals from Mexico for the period from 2011 to 2014. To identify the adverse drug reactions, the active pharmacovigilance was proposed. The causality analysis was performed by Naranjo algorithm and the severity of the adverse reactions was determined according to the Mexican official standard.
Results: 189 medical records were reviewed. Only 99 patients were included into the study, of whom 92 % had at least one adverse reaction related to chemotherapy. 718 adverse drug reactions were found, 346 (48.2 %) were associated with anthracyclines-based chemotherapy. The incidence of adverse reactions associated with anthracyclines-based chemotherapy was 68.7, 39.4, 37.4, 33.3, 25.0, 15.2 and 8.1 % for febrile neutropenia, thrombocytopenia, mucositis, anemia, cardiotoxicity, vomiting and diarrhea, respectively. Among adverse reactions associated with anthracyclines-based chemotherapy, 280 (80.9 %) were severe, 35 (10.1 %) were moderate and 31 (9 %) were mild.
Conclusion: This study has showed that the incidence of adverse reactions associated with antracyclines-based chemotherapy is high in paediatric population. The adverse reaction with highest incidence was febrile neutropenia and this reaction is considered as severe according to the Mexican official standard. These data can be used to evaluate the safety profile of Anthracyclines in paediatric patients and evaluate the costs of adverse reactions in paediatric hospitals.

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Unintended Central Nervous System Risks with Dextromethorphan in Different Indications. Preliminary Results; Systematic Review and Meta-Analysis of Randomised Clinical Trials

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Introduction: Dextromethorphan (DMP) is one of the active antitussive ingredients in many OTC products. Other indications have been studied in randomised clinical trials (RCTs) with DMP: amyotrophic lateral sclerosis, reduction of pain, sedation, detoxification of alcoholism, opioid withdrawal, seizures control, and treatment of pseudobulbar affect.
Aim: The aim of this systematic review and meta-analysis (SR&MA) is to provide the first reliable assessment of unintended effects in central nervous system (CNS) with the use DMP in RCTs.
Methods: This SR&MA protocol was registered with PROSPERO database (CRD42015016631). The search strategy involved RCTs using DMP in different indications, and spanned from January 1950 to April 2015 in Medline, EMBASE and Cochrane Library databases. This SR&MA was conducted following the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses), the Cochrane Handbook and the Cochrane Adverse Effects Methods Group. The outcomes of interest evaluated were the number of adverse events associated with a CNS physiopathology. The events reported were grouped in only one group as CNS events. Analysis of odds ratio (OR) as measure of effect and 95 % confidence intervals (CI95 %) and p values as generated from the chi-squared were calculated; heterogeneity was assessed using the I2 test. Subanalysis by DMP alone and DMP combinations vs placebo/comparator and by low ($\leq$60 mg/day), medium ($\leq$180 mg/day) and high ($>$180 mg/day) doses were performed.
Results: The searches returned 2,744 hits, two-hundred-and-five publications were selected for review and sixty-two RCTs included in the meta-analysis involving 6039 subjects. A total of 102 preferred terms (PTs) according to MedDRA coding were reported from which 44 PTs (43.1 %) involved a CNS physiopathology.
Five of six meta-analysis performed found evidence of association, statistically significant, with CNS events, the exception was DMP medium dose's group due to the fact that 6 RCTs recorded number of CNS events

for DMP which exceeded the number of subjects; impossibility of performing an OR analysis. The smaller association was in DMP (alone/combination) vs placebo/comparator group (sixty-two studies) with OR 1.33; CI95 % (1.07–1.66): $I^2 = 71.2$ %; $p = 0.01$. The stronger association was in DMP high dose group (>180 mg/day) with OR 2.56; CI95 % (1.26–5.22): I2=78 %; $p = 0.009$.

Conclusion: The results suggest evidence of associations for CNS events in five of six DMP groups. The sub-analysis by dose demonstrates these associations in the low and high DMP dose groups; there is a 120 % more CNS events in the high dose vs the low dose group. Further sub-analysis are planned contemplating decreasing heterogeneity to better understand these associations.

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Study of Compliance with the Isotretinoin Pregnancy Prevention Programme regarding Pregnancy Testing in France Using the EGB Database

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Introduction: Isotretinoin, an effective treatment in severe acne, is known to be a potent teratogen. The European Pregnancy Prevention Programme (PPP) includes a pregnancy test (PT) before each prescription and a final one 5 weeks after treatment discontinuation, and dispensing no later than 7 days post-prescription.

Aim: The main objective was to evaluate compliance with PT recommendations in France from 2007 to 2013 in new female isotretinoin users aged 11–50 years.

Methods: This was a retrospective cohort study using the EGB database, which provides sociodemographic characteristics and healthcare consumption data of a permanent representative sample of the population covered by the French national health insurance. Reimbursed PTs have been investigated in accordance with more or less stringent time intervals regarding prescription and dispensing. The link between the rate of PTs, patient characteristics and those of the course of treatment was estimated using logistic regression models.

Results: A cohort of 1 367 patients with a mean age of 25.4 years was identified. Almost 90 % received only one course of treatment. Compliance with PT recommendations is almost achieved at the time of treatment initiation (63–81 %). It is much lower for renewals (33–59 % subjects had all PTs) and very low after treatment discontinuation (12 %). Dermatologists issued 89 % of prescriptions. Prescriptions issued by general practitioners compared to dermatologists were associated with lower PT compliance, regardless of the treatment stage, i.e. initiation, renewal or post-treatment.

Conclusion: These results warrant a thorough evaluation of the PPP and the reasons behind poor compliance.

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Non Hemorrhagic Adverse Effects Of Fluindione: A Comparative Study with Coumarine Derivatives

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Introduction: Non hemorrhagic adverse drug reaction (ADR) associated with vitamin K antagonists (VKA) used in France (acenocoumarol, fluindione, warfarine) are often neglected. In particular, fluindione, the most commonly prescribed VKA in France, is associated with serious delayed type hypersensitivity reactions (DTH).

Aim: To better define the type of DTH induced by VKA and to estimate their incidence rate.

Methods: All cases of VKA-induced acute renal failure (ARF), severe cutaneous ADR, acute liver disorders (ALT > 5N and/or PAL > 1.7N), or isolated neutropenia (<1G/L) recorded by the French Pharmacovigilance centers and the marketing authorization holders from 01/2010 to 12/2013 were extracted. Prescription data were obtained from the EGB (Echantillon Généraliste des Bénéficaires), a permanent representative sample of the French national health insurance.

Results: 243 cases were retained (fluindione: 213; warfarin: 24, acenocoumarol: 6). Cutaneous reactions were the most frequent (36.6 %). Drug reaction with eosinophilia and systemic symptoms (DRESS) (42), complicated by renal failure in 61 % of cases, and acute generalized exanthematous pustulosis (7) were quite exclusively reported with fluindione. Vasculitis (27) was relatively more frequent with warfarin. ARF (33.3 %) were associated with histological lesions of tubulointerstial nephritis in all cases with available histological data and involved fluindione in 97.5 % of cases. Severe ARF (stage 4) was noted in 93 % of patients. Among the 84 patients with fluindione-induced ARF (including those with DRESS), a follow-up of renal function for more than 6 weeks after the acute episode was available in 37 patients and indicated persistent sequelae with a mean decrease in glomerular filtration rate from 66.7 to 44.2 ml/min ($p < 0.0005$). Other ADR consisted of acute cytolytic or mixed hepatitis (17.7 %) and moderate to severe neutropenia (12.3 %). Overall, AVK discontinuation after the first suggestive symptoms was frequently delayed, indicating that these ADR are still underrecognized. A switch to a coumarinic VKA performed in 79 patients with fluindione-associated DTH was well tolerated in 77. According to the EGB data, the overall reporting incidence rates per 10,000 new prescriptions was 1.77 [1.5–2.1] for fluindione, 1.11 [0.6–1.9] for warfarin and 0.42 [0.05–1.5] for acenocoumarol. After taking into account only cases with ARF, the incidence was more frequent with fluindione (1.34/104) than with warfarin (0.33/104) (OR (95 % CI): 4.06 [1.5–11.4]).

Conclusion: This study confirms that the non hemorrhagic ADR profile of fluindione differs from that of coumarine derivatives. As fluindione is the most frequently prescribed VKA in France, such practice is questionable and, to our opinion, warfarin should be preferred.

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Anti-tuberculosis Drug-Associated DRESS Syndrome: A Case Series

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Introduction: Although DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome associated with anti-tuberculosis drugs is very rarely reported, its diagnosis should not be dismissed. Its management implies an early withdrawal of suspected drugs and resorting to an often less effective second-line treatment.
Aim: To analyse the characteristics of anti-tuberculosis drug-associated DRESS syndrome and the most likely involved drugs.
Methods: All cases of DRESS syndrome (RegiSCAR score $\geq$4) related to first line anti-tuberculosis drugs notified to French Pharmacovigilance centres of Grenoble and Lyon between January 1st, 1995 and May 15th, 2015 were included and confirmed by a dermatologist from French RegiSCAR network.
Results: Among 13 cases retrieved, 9 (7 women including 1 HIV-positive patient) with a mean age of 56 years (29–73) were included in our study. Seven patients received a first-line anti-tuberculosis treatment including rifampicin, isoniazid, pyrazinamide and ethambutol and two a tritherapy without ethambutol. Mean time to onset of first symptoms after starting treatment was 30.2 days (11–72) and potential suspected drugs were withheld within a median of 3 days (0–25). All patients had fever $\geq$38.5°C and eosinophilia $\geq$1.5G/L (1.5–9.28). Liver was the most frequently involved internal organ (n = 7, requiring liver transplant in one case) following by bone marrow (n = 3), lung (n = 2), kidney (n = 1) and central nervous system (n = 1). In all cases, the cutaneous eruption was either maculopapular or erythematous, included marked facial edema in 4 patients. Skin biopsy performed in 5 patients was compatible with DRESS syndrome. Outcome was favourable in all cases. According to the French drug reaction assessment method, rifampicin (n = 6) and isoniazid (n = 6) were the most frequently suspected drugs. Patch tests were positive in 3 cases (isoniazid n = 2, ethambutol n = 1). No culprit drug was reintroduced afterwards. In 5 patients for whom patch tests were either negative (n = 2) or not performed (n = 3), careful reintroduction of anti-tuberculosis drugs led to a relapse (one experienced 2 relapses after rifampicin then pyrazinamide).
Conclusion: Even if patch tests are useful to identify the culprit drug in DRESS syndrome, discrepancies between positive reintroduction and negative results of skin tests in 2 patients suggest a non-specific relapse of DRESS syndrome or a lack of sensitivity of patch tests, especially if they are performed closely to the acute phase. Most limitations of our study are related to a retrospective analysis.

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VigiAccess—e Public Key to The WHO ICSR Database

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VigiBase® is the WHO global ICSR database; it consists of reports of adverse drug reactions (ICSRs) received from member countries in the WHO Programme for International Drug Monitoring (PIDM) since 1968. VigiBase is continuously updated with incoming reports and is the largest and most comprehensive source of ICSRs in the world. It is developed and maintained by the Uppsala Monitoring Centre (UMC) on behalf of the World Health Organization. By May 2015 the database contained around 11 million ICSRs.
VigiBase is a computerised pharmacovigilance system, in which information is recorded in a structured, hierarchical form to allow for easy and flexible retrieval and analysis of the data. The case reports in VigiBase are anonymized and do not allow to identify neither the patient nor the reporter. Its purpose is to help detect and characterize potential medicine safety hazards.
Until recently only WHO PIDM members could access VigiBase data directly. The World Health Assembly together with WHO, aware of the need for more transparency, supported the opening of the VigiBase data to a broader public. This has now been achieved with VigiAccess, a tool that allows the public to retrieve statistical data from VigiBase.
UMC is currently exploring the possibility of leveraging the same data as retrievable through VigiAccess in a way which will allow a seamless integration of such a dataset in other pharmacovigilance systems.
This session shows how the VigiAccess tool has been uncoiled and what it can provide. It also shows current activities aiming at the delivery of the data in a format suitable for integration in other systems.
About the UMC
Since 1978 Uppsala Monitoring Centre has played a major role in the development of patient safety globally. As a worldwide leader in the science of pharmacovigilance, UMC advances patient safety by exploring and understanding the benefits and risks of medicines to help patients and physicians make wise therapeutic decisions.

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Use-Case for Big Data Technology in Pharmacovigilance

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Introduction: BIG DATA is a technology buzz-word that we hear a lot these days, often in the area of healthcare, specifically relating to the analysis of huge volume of electronic patient records collected by

insurance companies and hospital systems. The technology promises the ability to perform unstructured, Google-like searches and other advanced analytics against these gigantic data sets with interesting and actionable results appearing in the blink of an eye. As it turns out, there are a lot of use-cases for BIG DATA technology in Pharmacovigilance around the publicly available medical product safety data.

Aim: To discuss the use of BIG DATA technology to improve the process of managing and performing analytics on adverse event report data from all sources.

Methods: In this presentation, we will provide a very high level concept of BIG DATA technology, a roadmap for implementing a BIG DATA program within a national agency's or pharmaceutical company's Pharmacovigilance department, and details of a number of real world use-cases for BIG DATA technology tightly integrated with a commercial Pharmacovigilance system.

Results: The use cases for implementing a BIG DATA program for adverse event report data include:

- Natural language search of safety data
- Simple, powerful data analytics
- Cluster analysis based on geo-coded case data
- Advanced synonym management
- Automation of the creation of an initial case from the narratives and source documents
- Quality assurance checks
- Advanced duplicate search
- Case triage and prioritization

Conclusions: There is a compelling need to approach the pharmacovigilance process and the resulting adverse event report data with a variety of modern tools and technologies. The use of BIG DATA technology will provide regulatory authorities and pharmaceutical companies with a new and interesting perspective on the kinds of process automation and analytics they can expect from the latest technology.

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New Oral Anticoagulants: What Do their Adverse Drug Reactions Reports Suggest?

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Introduction: The new oral anticoagulants (NOACs), such as apixaban, dabigatran and rivaroxaban, are commonly used as an alternative to the vitamin K antagonists. In addition to the concerns associated with any new medicine, NOACs lack easily available laboratory monitoring tests of anticoagulant activity and their antidote are in development [1]. In this context, independent postmarketing pharmacovigilance studies are indispensable to better know bleeding disorders associated with their use.

Aim: To describe the hemorrhagic and thrombotic reported ADRs of NOACs.

Methods: NOACs reports included in the PeriWeb database system of the Health Surveillance Center of São Paulo (CVS), the most important pharmacovigilance centre of Brazil, from March 2009 to December 2014 were analysed. The ADRs were categorized using the World Health Organization Adverse Reactions Terminology (WHOART).

Results: As shown in Table 1, reports of bleeding events in patients receiving NOACs are not rare, as more than 500 episodes have been reported to the CVS. The differences in absolute numbers between active ingredients can be explained by the different marketing time and consumption. Notwithstanding, there are no significant differences in the proportion of reported bleeding episodes.

Table 1 ADRs related to NOACs identified from Health Surveillance Center of São Paulo

Marketing year NOAC ADRs	2009 Rivaroxaban n (%)	2008 Dabigatran n (%)	2011 Apixaban n (%)
Hemorrhages	310 (20.1)	174 (25.6)	24 (24.0)
Thrombosis	206 (13.3)	83 (12.2)	5 (5.0)
Indicative of bleeding	105 (6.8)	32 (4.7)	2 (2.0)
Other ADRs	923 (59.8)	391 (57.5)	69 (69.0)
Number of patients	695	329	56

Conclusion: Bleeding and thrombosis episodes in patients treated with NOACs are commonly reported to the CVS. While new coagulation tests for these medicines are not developed, the best way to avoid unnecessary risk for the patients is to use rivaroxaban, dabigatran and apixaban strictly according to their approved indications, and taking into account patients' renal function and concomitant medication.

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Study of Iodinated Contrast Media induced Anaphylaxis Based on Korea Adverse Event Reporting System, 1989–2013

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Introduction: Iodinated contrast media (ICM) is widely used for diagnosis with computed tomography (CT) and it is used in healthy population as well. Hypersensitivity in ICM rarely occurs but is an immediate reaction and unpredictable. Especially, anaphylaxis which is a serious allergic reaction, could lead to death [1, 2].

Aim: This study is aimed at evaluating the safety profile of anaphylaxis related to ICM.
Methods: Korea Adverse Event Reporting System (KAERS) database from January 1, 1989 to December 31, 2013. Was used for this study. The types of ICM were selected in ATC 3RD Level (V08A: X-RAY CONTRAST MEDIA, IODINATED). Also, 3 Preferred Terms, i.e. "anaphylatic shock", "anaphylactoid reaction", "anaphylaxis reaction", were selected in the WHO-ART High level term as "Anaphylaxis reaction". Safety profiles were compared between different ICMs using the proportional reporting ratio (PRR) and the 95 % confidence interval (95 % C.I.) [3].
Results: A total of 478,633 Individual Case Safety Reports (ICSRs) were reported from 1989 to 2013. Of those ICSRs, we constructed a dataset which was included 457,980 ICSRs through inclusion/exclusion criteria. In the dataset, a total of 354 ICSRs were related to the ICM induced anaphylaxis. Among the 354 ICSRs, PRR of the ICM induced anaphylaxis were higher than the other types of ICM [Iodixanol (PRR, 4.31; 95 % CI, 2.99–6.20), Iopromide (PRR, 3.29; 95 % CI, 2.86–3.78) and Ioversol (PRR, 3.14; 95 % CI, 2.10–4.68)].

Table 1 Safety profiles of ICM induced anaphylaxis by type of ICM, 1989–2013

Type of ICM	No. of ICSRs	PRR (95 % CI)	CHISq
diatrizoic acid	1	11.65 (1.60, 84.84)	9.76
iohexol	48	1.50 (1.13, 1.99)	7.91
iopamidol	24	1.46 (0.98, 2.18)	3.49
iopromide*	189	3.29 (2.86, 3.78)	283.81
ioversol*	24	3.14 (2.10, 4.68)	34.78
iodixanol*	29	4.31 (2.99, 6.20)	73.17
iomeprol	37	1.89 (1.37, 2.61)	15.46
iobitridol	5	0.49 (0.20, 1.18)	2.66
iopydol	2	113.64 (22.94, 562.84)	223.65

* Detected as signal

Conclusions: The signal of ICM induced anaphylaxis were detected through this safety evaluation and further review process is needed through the Electric Health Record (EHR) in medical institutions or large health insurance claim data.
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Pharmacovigilance Network, a Tool Kit for Enhancing Risk Management; Lessons Learned from Thailand

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Introduction: Pharmacovigilance (PV) is known as the activity of monitoring the safety of medicines and taking appropriate action to minimize risk. PV network are being initiated and enhanced PV and risk management system. The drug related problems (DRPs) detected through network are very important to take appropriate decision by drug regulators to safeguard public health.
Aims: To describe a PV network is one of key success factor for detecting DRPs and enhancing the drug regulation.
Methods: "Chiang Mai PV Network", the three-party network consisting of the Faculty of Pharmacy, the Provincial Public Health Office and the 24 community hospitals across Chiang Mai province, was established. Pharmacists play a major role in this network. The network meeting is held every 2 months to continually motivate clinical and professional skills on drug monitoring and strengthen PV system in their setting. DRPs detected across the network were discussed on a root-caused analysis. The performance were collected to evaluate the national risk management impact.
Results: Two serious cases were detected. The first one was herbal bolus for pain relief induced Toxic Epidermal Necrolysis with dead outcome. After investigating, it was indicated the product was adulterated with various modern medicine. Finally, the collaboration with Thai FDA, drug regulatory authority, the illegal manufacture was arrested. For the second case, it was the inappropriate use of camphor injection by non-health care professional resulted in death. The case was reported to Thai FDA, National Vigilance Center. The product was reassessed on risk and benefit. The Marketing Authorization Holders (MAHs) were requested the evidence to demonstrate the product efficacy and distribution. In conclusion, the Drug Committee adopted the PV advisory subcommittee's recommendation on withdrawal of all camphor/sodium camphosulphanate containing products, because of its benefit did not outweigh the risk. The Ministerial Decree of Ministry of Public Health was issued to withdraw from the market. These two cases shown that PV network activities could have an effect on national risk management.
Conclusion: PV activity continues to play a specialized and crucial role in ensuring ongoing safety of medicine. PV network should be considered as one of an important strategy for enhancing PV and risk management system in every country.
Keywords: Pharmacovigilance, Network, Risk management

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Evolving Nature of Evidence in Pharmacovigilance to Inform on Regulatory Decision Making

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Introduction: Observational data are frequently being used as a source of information to evaluate the safety of drugs in the 'real world' setting; these studies have successfully contributed to the drug safety decision-making process. Historically, however, it has been argued that observational data are not "robust" enough to be used in the assessment of drug safety as

they may be prone to different sources of bias. Even well-designed and well-conducted observational studies are often viewed with skepticism. In this view, some have argued that randomized controlled trials (RCTs) are the most powerful and only tool for doing so.

Aim: The goal of the current presentation is to discuss the evolving role observational data have played in informing on regulatory decision making related to drug safety. This is particularly important given the increased focus on risk management planning worldwide and the growing need for rapid response to safety questions and signal identification.

Methods: Not applicable.

Results: The presenter will provide examples of situations where observational data alone or in combination with RCTs has provided appropriate evidence to support regulatory decision making. The regulatory actions have included product withdrawal, updates to the product label, risk identification and characterization, in addition to the evaluation of effectiveness/burden of risk minimization activities. Moreover, the type of observational data used in pharmacovigilance has evolved throughout the years. Historically, pharmacovigilance has utilized spontaneous reports of adverse events to identify drugs needing more detailed scrutiny and attention. However, recent years have witnessed the increased use of electronic health care databases to assess post-authorization benefits and risks in populations that are using the medicine.

Conclusions: Emergence of methodological expertise has increased standards in post-authorization studies which have raised confidence in observational data. In particular, there is growing use of multiple sources evidence to support regulatory authority activities. Therefore, awareness and correct interpretation of all available data about the relation between drug and disease is a prerequisite for an objective risk–benefit analysis.

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Practical Aspects of Developing Relevant Key Performance and Quality Indicators (KP-QIs) for Risk-Based Quality Management in Pharmacotherapy

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Introduction: Besides being a new expectation by regulatory agencies under good clinical practices, Quality by Design (QbD) and Risk-Based Quality Management (RBQM) concepts are receiving attention worldwide. According to FDA and EMA guidelines, Key Risk Indicators (KRIs) and Critical to Quality (CTQ) metrics should focus on safety of research subjects and data integrity [1, 2]. Biological products, due to their nature, can increase risks while being tested in clinical trials [3].

As the industry's utilization of risk-based monitoring continues to increase along with the development and expansion of the area of RBQM, the need for the integration of these two concepts in pharmacovigilance becomes apparent. The premise behind RBQM is that monitoring quality can improve by leveraging existing data intelligence. (1) RBQM requires development of relevant metrics, key risk and quality indicators, as well as a solid process for review/follow-up of the identified safety signals [1, 2].

Aims: Utilize principles of Quality by Design (QbD), develop and test relevant metrics as quality and performance indicators for Risk-Based Quality Management (RBQM) systems.

Methods: We have established QbD parameters and RBQM metrics and attempted to build them into our clinical operations. Practical aspects of developing key safety and quality indicators at all stages of clinical trials will be discussed.

Results: Deviations from the study protocol can lead to compromised patient safety and inaccurate data, placing the trial at risk.

Our analysis showed that many of the deviations were repetitive, where the same errors were made continuously (i.e. 27 of the 79 deviations, or 34 %, were related to a malfunctioning camera that was not repaired promptly). An analysis of the number of deviations per active patient over time was conducted which provided insight into temporal trends as well as the effect of study coordinator changes on the number of protocol deviations.

Conclusions: Proactive assessment of safety in studies with biologics can lead to earlier mitigation of risks, quality improvement in data obtained, and increased quality of studies conducted in this field. An understanding of the frequency and types of adverse events can provide an expectation for those conducting trials in a particular indication.

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Implementation of Quality by Design (QbD) and Quality Risk Management (QRM) Strategies in Pharmacovigilance for Wound Care Trials

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Introduction: Quality by Design (QbD) and Quality Risk Management (QRM) concepts have emerged from manufacturing to clinical operations. A risk-based approach for signal detection in pharmacovigilance requires not only a strategy but tools to define key indicators to measure specific risks. As reference from the recent FDA and EMA guidelines, Key Risk Indicators (KRIs) and Critical to Quality (CTQ) metrics should focus on safety of research subjects and data integrity [1]. The ability to predict potential issues in compliance, safety and to develop strategies to reduce these risks is a valuable asset in clinical trial management [1, 2].

Aim:

- Identify trends in safety factors and adverse event occurrence by type
- Establish correlation of wound etiology with specific safety concerns

Methods: An audit of several prospective, randomized wound care clinical trials was performed. These studies have similar objectives, study design, eligibility criteria, and outcomes. The rate of serious adverse events (SAEs) was assessed and compared between two wound types: diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs). Adverse events were classified into categories to better understand the correlation between type of event and wound etiology.

Results: A comparison of SAE occurrences between DFU and VLU studies showed an average of 2.1 SAEs per patient in the DFU studies and 1.6 SAEs per patient in the VLU studies. The most common SAE for both

DFU and VLU was wound infection. DFU patients had a higher prevalence of gastrointestinal problems and infections unrelated to the wound as compared to the VLU counterparts.

Conclusion: Proactive assessment of potential difficulties in prospective wound care studies can lead to earlier mitigation of risks, quality improvement in data obtained, and increased efficiency of studies conducted in this field.

An understanding of the frequency and types of adverse events can provide an expectation for those conducting trials in a particular indication: a larger number of serious adverse events per patient on averagecan be expected for patients with diabetic foot ulcers, and that these events will be more diverse as compared with venous leg ulcer patients.

Optimization of research staff number, training and experience are crucial to reduce protocol deviations and improve study conduct overall.

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