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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

ABSTRACTS

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Adis

INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

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P001

Evaluation of Pattern, Predictability, Severity and Preventability of Adverse Drug Reactions in Department of Pharmacology

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Introduction: Adverse drug reactions (ADRs) associated with psychotropic drugs leads to noncompliance, increased morbidity and higher economic burden. There is growing concern to assess the ADRs which is a hindrance in achieving successful remission.
Aim: To analyze the pattern, causality, preventability, severity and predictability of occurrence of ADRs.
Method: This observational study was carried out from 2012 to 2016 to analyze the ADRs reported spontaneously from the Department of Psychiatry at Victoria Hospital to the ADR monitoring Centre. Patient demographics, clinical and drug data, details of ADR, onset time, causal drug details, outcome and severity were collected as per CDSCO-ADR reporting form. Causality was assessed by WHO-ADR probability scale, preventability by Modified Schumock and Thornton scale and Severity by Hartwig and Siegel Scale.
Results: A total of 81 ADRs were reported in 5 years. 40.7 % of the ADRs were observed among 31–40 years. Majority of ADRs were noted among patients with depression (34.5 %), followed by schizophrenia (28.3 %). Central nervous system (58 %) was affected predominantly. Headache (12.3) was the most common ADR, followed by dystonia (11.1 %) and drowsiness (9.9 %). Dystonia was seven times more common in patients with conventional antipsychotics. Antidepressants (48 %) and antipsychotics (37 %) caused higher frequency of ADRs. Patients with antipsychotics encountered 1.8 times more ophthalmic ADRs than antidepressants. Fluoxetine (17 %) accounted for most of the ADRs, followed by risperidone (12.3 %). Occurrence of diarrhea was two times more frequent with fluoxetine than amitriptyline. 85 % of the ADRs were of 'probable' causality and 5 % were unpredictable. Two unpredictable ADRs: amitriptyline induced desquamative erythematous rash and escitalopram induced arthralgia. 9 % of the ADRs were severe: haloperidol induced dystonia, chlorpromazine induced neuroleptic malignant syndrome, amitriptyline induced desquamative erythematous rash and isoniazid induced psychosis. Serious ADRs were noted 1.9 times more among the patients prescribed with conventional antipsychotics over newer antipsychotics. Majority (74 %) of the ADRs were probably preventable. 44 % of the ADRs required additional medical treatment, while causative drug was withdrawn in 36 %. 96.3 % of the patients recovered completely.
Conclusions: A wide spectrum of ADRs affecting the CNS, gastrointestinal, cardiovascular, metabolic and hematopoietic system were reported. Rare adverse events like Clozapine induced thrombocytopenia, escitalopram induced arthralgia and risperidone induced perioral tremor were observed. Conventional antipsychotics lead to serious ADRs 1.9 times more. Antipsychotics caused 1.8 times more ophthalmic ADRs than antidepressants. Though 5 % of ADRs were serious, no mortality was noted which highlights the appropriate management of ADRs at our Centre.

P002

Profile of Serious Adverse Drug Events in a Tertiary Care Hospital of South India—a Five Years Example

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Introduction: Adverse drug event (ADE) is said to be serious, when it is life-threatening, leads to hospitalization, disability, congenital anomaly, death or requires intervention to prevent permanent impairment or damage. Early detection and timely management of serious ADEs reduces mortality. Hence, the present study was undertaken.
Aim: To determine the pattern, causality, preventability of serious ADEs reported to adverse drug reaction (ADR) Monitoring Centre of Bangalore Medical College and Research Institute.
Method: This observational study was carried out to profile serious ADEs reported from hospitals attached to Bangalore Medical College and Research Institute to ADR Monitoring Centre, under Pharmacovigilance Programme of India from 2012 to 2016. Patient demographics, clinical and drug data, details of the ADE, onset time, causal drug details, outcome and severity were collected as per CDSCO form. Causality was assessed by WHO-ADR probability scale, preventability by modified Schumock and Thornton scale.
Results: A total of 809 ADEs were reported, out of which 50 (6.18 %) were found to be of serious in nature. Male preponderance (74 %) was observed. Most (42 %) of the serious ADEs were noted among the patients of age group of 20–40 years. Maximum serious ADEs were reported from the Department of Dermatology (56 %), followed by Neurology (12 %) and Antiretroviral Therapy (ART) Centre (10 %). Steven Johnson Syndrome (SJS) (20 %) contributed the most, followed by hepatotoxicity (18 %) and exfoliative dermatitis (14 %). Antiepileptic caused maximum number of serious ADEs (32 %), followed by anti tubercular therapy (ATT) (18 %) and ART (18 %). On WHO causality scale, 76 % of the ADEs were found to be 'probable'. Life threatening ADEs was 56 and 86 % required intensive intervention. Patients admitted due to ADEs were 84 % while 16 % of patients experienced severe ADEs during hospital stay. 4 % of serious ADEs were definitely preventable. SJS was seen 2.72 times more with antimicrobials than antiepileptic. Hepatotoxicity was observed 10.2 times more with ATT as compared to ART.
Conclusions: Serious ADEs constituted 6.18 % of all ADEs reported, of which 4 % were definitely preventable. Majority of patients recovered and no mortality was noted. SJS was more commonly seen with antimicrobials and hepatotoxicity with ATT. India harbors the majority of patients with epilepsy (10 million) and tuberculosis (2.2 million) in the world that may explain higher frequencies of serious ADEs to antiepileptic and ATT. This study highlights the importance of monitoring and timely management of serious ADEs to most commonly prescribed medications in India.

P003

Cutaneous Adverse Drug Reactions from a Teaching Hospital in Bengaluru: An Observational Study to Dermatology

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Introduction: Cutaneous adverse drug reactions (CADRs) are frequent manifestations of drug reactions and a major health problem worldwide. There is a wide spectrum of CADRs ranging from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN), leading to discontinuation of treatment, impaired quality of life and increased economic burden. Knowledge of drugs that cause CADRs can help physicians in choosing safer drugs.
Aim: To determine the clinical spectrum, causality, severity and preventability of CADRs.
Method: An observational study was carried out from 2012 to 2016 to analyze the CADRs reported spontaneously from Dermatology Department, attached to Bangalore Medical College and Research Institute to ADR Monitoring Centre, under Pharmacovigilance Programme of India. Patients' demographics, clinical and drug data, details of ADR, onset time, causal drug details, outcome and severity were collected as per CDSCO form. Causality was assessed using WHO-ADR probability scale, severity using modified Hartwig and Siegel severity scale and preventability using modified Schumock and Thornton scale.
Results: A total of 809 ADRs were reported, of which 230 (28.4 %) were CADRs. There was a male preponderance (56 %). The age group of 21–40 years (57 %) was most affected. Maximum number of CADRs was seen with beta lactam class of drugs (20 %), followed by NSAIDs (17.4 %) and antiepileptics (13.5 %). Among the CADRs, maculopapular rash (26 %) was the most common, caused by Nevirapine (35 %) followed by Phenytoin (17 %). Stevens Johnson syndrome (SJS) was the most frequently observed severe CADR, commonly associated with Phenytoin (45.5 %) and Diclofenac (18.2 %). The odds of developing SJS was 2.75 times more with Phenytoin compared to Diclofenac. The causative drug was withdrawn in 90 % of cases. 86 % of cases were managed with additional treatment. No mortality was noted. Causality assessment indicates 80.4 % as probable and 19.6 % as possible. Majority (81 %) of the CADRs was of moderate severity and 6 % were severe like clobazam induced erythema multiforme and dapsone hypersensitivity syndrome (DHS). Preventability scale indicates 86.5 % to be 'not preventable' and 11 % to be 'definitely preventable'.
Conclusions: A wide clinical spectrum of CADRs was observed. Definitely preventable CADRs were found to be due to absence of recording previous history of drug allergy and wrong choice of self-medication by the patients. Inconsistent with the previous literature, incidence of Diclofenac induced SJS was high in the present study. Though the mortality reported for DHS is high, it was prevented by timely diagnosis and management in our Centre.

P004

Comparing the Adverse Drug Reactions of Conventional vs. Newer Antiepileptic Drugs: An Observational Study

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Introduction: Neurological disorders have been estimated to account for up to 20 % of the nationwide cost of healthcare in developing countries. There is growing concern to assess the adverse drug reactions (ADRs) of anti-epileptic drugs (AEDs), which have an impact on compliance, economic burden and quality of life. AEDs have broad spectrum of effects, need long term therapy leading to wide range of ADRs. Thus, the present study was undertaken.
Aim: (1) To assess the incidence, severity, and causality of ADRs due to AEDs and (2) to compare the pattern of ADRs caused by conventional vs. newer AEDs.
Method: This observational study was carried out from 2012 to 2016 to analyze the ADRs reported spontaneously from Department of Neurology at Bangalore Medical College and Research Institute to ADR monitoring Centre. Patient demographics, clinical and drug data, details of ADR, onset time, causal drug details, outcome and severity were collected as per CDSCO ADR reporting form. Causality was assessed using WHO-ADR probability scale, preventability by Modified Schumock and Thornton scale and severity using Hartwig and Siegel Scale. Predictability was categorized as Type A and Type B ADRs.
Results: 85 ADRs were reported in 5 years, with maximum from 21 to 40 years and female predominance (24 %). Conventional AEDs (75 %), mainly phenytoin (40 %) and carbamazepine (27 %) contributed the most. Amongst newer AEDs, Levetiracetam accounted for maximum ADRs (13 %) followed by Gabapentin (10 %). ADRs affecting central nervous system (CNS) (65 %) were predominant in both groups. Newer AEDs caused Giddiness 10.7 times more frequently than conventional ones. Erythematous rash was 1.71 times more in the conventional drugs than newer ones. Frequency of drug withdrawal was higher among the patients on conventional AEDs (60 vs. 30 %). Causality assessment indicated that 90 % were probable and 10 % were possible. Majority of the ADRs in both the groups were of moderate severity (50 %). The severe ADRs (7 %) seen only with conventional AEDs were hepatotoxicity and pancreatitis due to sodium valproate and hyponatraemia due to carbamazepine. Definitely preventable ADRs (12 %) were noted among both the groups. No mortality was reported.
Conclusions: Serious ADRs were seen with only conventional AEDs. Patients with serious ADRs (7 %) were treated successfully with no mortality. Definitely preventable ADRs (12 %) could have been prevented with dose titration. Lack of serious ADRs by newer AEDs highlights its safety.

P005

Adverse Drug Profile of Antimicrobial Agents in a Tertiary Care Hospital: A Retrospective Study

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Introduction: Adverse drug events (ADEs) are the recognized hazards of drug therapy. About 20–50 % of the hospitalized patients receive Antimicrobial agents (AMAs), of which 35–40 % may develop ADEs in India. Early detection and treatment can reduce the incidence of ADEs and contribute towards better health care.
Aim: To identify the patterns, predictability, preventability and outcomes of ADEs caused by AMAs in a Tertiary Care Hospital.
Method: A retrospective observational study was carried out to analyze the ADEs due to AMAs reported spontaneously from hospitals under Bangalore Medical College and Research Institute to ADR Monitoring Centre under Pharmacovigilance programme of India from 2012 to 2015. Patient demographics, clinical and drug data, medication history, ADE history, and other relevant details were collected as per CDSCO form. Causality was assessed by WHO ADR probability scale, preventability by modified Schumock and Thornton scale and severity by Modified Hartwig and Siegel scale.
Results: 100 ADRs caused by AMAs were reported spontaneously during the study period. Male predominance (58 %) with majority (57 %) from age group of 21 to 40 years was noted. ADRs reported were mainly dermatological (38 %), followed by gastro-intestinal (34 %). Maculopapular rash (35 %) contributed the most. Cephalosporin (35 %), fluoroquinolines (20 %), antitubercular drugs (16 %), penicillin (16 %) and macrolides (9 %) contributed to the ADRs. Cutaneous adverse drug reactions were noted 1.62 times more in patients receiving fluoroquinolones over cephalosporin. ADRs affecting GIT was observed eight times more frequently with macrolides compared to penicillin. 78 % of the ADRs were of probable causality. 67 % of ADRs were unpredictable, 5 % were definitely preventable and 72 % were of moderate severity. Serious ADRs reported were 4 %. Causative drug was withdrawn in 80 and 78 % of the patients recovered after medical treatment.
Conclusions: Most of ADRs were caused by cephalosporin but, flouroquinolones were implicated in causing cutaneous ADRs more than cephalosporin. As suggested by literature, macrolides caused more gastrointestinal ADRs than penicillin. Oral (60 %) administration of AMAs lead to higher frequency of ADRs compared to parenteral (38 %). Definitely preventable ADRs were found to be due to lack of documentation of previous history of drug allergy. Majority of the patients recovered with medical treatment of the ADRs. This study highlights the importance of early detection and treatment of ADRs in leading to favourable outcomes.

P006

Misoprostol Misuse: The Moroccan Experience

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Introduction: Misoprostol is a synthetic PGE1 analog which is indicated in reducing the risk of NSAID-induced gastric ulcers in patients at high risk. This drug has many off label uses. Gyneco-obstetrical off label indications of this substance have many issues.
Aim: We reviewed the records of misoprostol misuse in the Moroccan Pharmacovigilance database.
Method: ARTOTEC and CYTOTEC are proprietary medicinal products which contain Misoprostol and were marketed in Morocco respectively in 2007 and 2009. We have had recently cases of misuse of ARTOTEC. Three women attempted to abort themselves by taking ARTOTEC orally, whereas, one patient had inserted the pills in her vagina.
Results: The outcome was fatal in two women, whereas, the abortion was successful in the third woman and the fourth patient was saved with her fetus.
Conclusions: Further development of medical methods for pregnancy termination and their introduction into national programmes must be taken. Besides, the quality of contraceptive, abortion services and partner communication must be improved.

P007

Comparison of Adverse Drug Reactions (ADRs) Reported by Patients Before and After the Amending of the French Legislation

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Introduction: According to the European Directive 2010/84/UE, the French legislation allows, since June 2011, patients and associations of patients to report ADRs to the Pharmacovigilance (PV) centers. Published data have shown that patients provide additional information to ADRs reported by health care professionals [1]. However, few data are available on the evolution of reported ADRs by patients.
Aim: Comparing the number and the quality of patients ADRs reports during two periods of 5 years before and after the amending of the French legislation in June 2011.
Method: We performed a retrospective study to compare the ADRs reported by patients and associations of patients between a first period (P1: 01/06/2006 to 31/05/2011) and a second period (P2: 01/06/2011 to 30/04/2016). We assessed reports recorded by 2 Pharmacovigilance centers of the Pharmacovigilance coordination of Ile-de-France, covering a population of more than 4.7 million of inhabitants of Paris area. We compared the number of ADRs reported, characteristics of patients, source of reporting (patient, patient's relatives or patient associations), incident (reporting less than 1 year after the onset of ADRs) or retrospective cases, reporting form (letter, email, phone …), characteristics of ADRs (number per case, organ classes, seriousness, expectedness), and finally the drugs involved (therapeutics classes, princeps or generics). The vigiGrade completeness score [2] was used to investigate the informativity of each case. We performed t-tests and ANOVA analysis.
Results: During P1, 194 reports (2.7 %) were reported by patients out of a total of 7106 cases, and 717 (7.5 %) during P2 out of a total of 9575 cases. Characteristics of patients and qualitative data for the two periods were presented.
Conclusions: An increase of 174 % was observed during P2. Most reports originated from females and patients themselves. New tools of

communication, email and Pharmacovigilance website, were used during P2. Most of ADRs were incident, expected and non-serious. Patient's reporting was influenced by media coverage of Pharmacovigilance issues: the H1N1 influenza vaccine campaign (P1), benfluorex (P1 and P2), and oral contraceptives (P2). The increase of reporting was balanced by a decrease of documentation of cases. The main factors impacting the vigiGrade score were: time to onset, therapeutic indication and outcome. Patients are adherent to report ADRs which contributes to the drug safety. To maintain a good documentation of cases, the Pharmacovigilance centers must be careful on the major items and recall patients to complete their report.

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P008

Prevalence of Adverse Drug Reactions Among HIV/AIDS Patients on HAART in University of Maiduguri Teaching Hospital, Nigeria; a Four Year Retrospective Study

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Background: Current evidence on antiretroviral therapy indicates that each person will have to take the drugs for the rest of their lives [1]. In Nigeria since 2000, the prevalence of HIV has shown gradual but consistent decline from 5.0 to 4.1 % in 2003 and 2010 following the introduction of highly active antiretroviral therapy (HAART) and massive campaigns [2, 3]. As HAART improves the quality of life among HIV patients; the adverse drug reactions (ADRs) associated with their use may lead to reduced quality of life in some patients.

Aims: To assess the prevalence, types and the determinants of ADRs among the cohort.

Methods: We performed a retrospective study at APIN Ltd Clinic, University of Maiduguri Teaching Hospital Nigeria, in ART naive adult patients recruited from January 2006 to December 2010 and followed up for 48 months from commencement of HAART. From the database and clinical charts of eligible patients, we extracted the socio-demographic and clinical information, type of reported ADRs, their date of onset, and physician's decision on whether or not ADRs was serious according to ICH E2A guidelines. Data was entered into excel sheets and analysed using SPSS IBM Ver. 21 statistical software package [4]. The main outcome of interest was ADR. Logistic regression was used to calculate odds ratios (OR) and of ADR associated with patient and treatment characteristics.

Results: A total of 7260 patients were initiated on HAART in the review period. The prevalence of suspected serious adverse events was 53.4 %. Most common ADRs were peripheral neuropathy (11.0 %), itching (9.5 %), anaemia (9.2 %), dyspepsia (9.1 %) skin rashes (9.1 %), and various forms of dermatitis (5.5 %). Neuropsychiatric manifestations [such as depressive disorders (0.75 %), morbid nightmares (0.7 %), hallucinations (0.6 %), anxiety disorder (0.62 %), psychosis (0.5 %) and aggressiveness (0.5 %)] were recorded. Almost all (96 %) the reported ADRs occurred between 3 and 18 months on treatment. Patients initiating on a zidovudine and efervirenz based regimen (P = 0.015, *P= 0.020*, respectively), baseline CD4 $\leq$ 200/mm^3 (P = 0.000), unemployed patients (*P = 0.000*), students (*P = 0.000*) and petty traders (*P = 0.000)* were statistically significantly associated with increase occurrence of an ADR.

Conclusions: The study has identified the prevalence, types and the determinants of ADRs among HIV/AIDs patient receiving care at APIN Ltd Clinic, University of Maiduguri Teaching Hospital, Nigeria. This finding might help establish clinical guidelines that emphasize drug toxicity profile as a major criterion for choosing HAART drugs, hence promoting Pharmacovigilance of ARV in Nigeria.

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P009

Causality, Severity and Preventability Profiling of Adverse Drug Reactions Among Medicine Inpatients

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Introduction: Adverse drug reactions (ADRs) represent the risk associated with the anticipated benefits of drug therapy and are known to be leading cause of morbidity and mortality worldwide. ADRs constitute an enormous clinical and economic burden on health care system. Evidence also suggests that approximately half of the ADRs are preventable.

Aim: This study was aimed to characterize the ADRs and to assess their causality, severity and preventability.

Method: This prospective observational study was conducted in the patients admitted to medicine wards of a public teaching hospital. Patients of all age groups and either sex admitted in medicine wards were included in this study. Those not willing or able to give informed consent were excluded. The causality of ADRs was assessed using Naranjo's scale and WHO-UMC criteria. Severity and preventability were assessed using modified Hartwig's severity scale and modified Schumock and Thornton criteria, respectively.
Results: Over the period of 6 months, data from 808 patients was collected. Of which 776 (486 male, 290 female) were analysed as they met the inclusion criteria. Out of 776 patients with complete documentation, 77 patients (45 male, 32 female) developed 82 ADRs during their stay in hospital with an incidence of 9.9 %. 65.8 % ADRs were observed in adults and 34.2 % in geriatrics. Maximum number of ADRs was observed in age group of 40–49 years (25.6 %). The highest number of ADRs were associated with antimicrobial drugs (24.4 %) followed by diuretics (15.80 %), opioid analgesics (14.6 %), anticoagulants (14.6 %) and antidiabetics (13.4 %). Among the organs affected, approximately half of the ADRs were associated with GIT (46.3 %) followed by metabolic (35.3 %), haematological (14.6) and cutaneous (9.7 %). Constipation (19.5 %) followed by hypokalemia (19.5 %), coagulopathy (14.6 %), hypoglycaemia (13.4 %) and hypersensitivity reactions (9.7 %) were most commonly observed ADRs. Causality assessment by Naranjo's scale revealed that 13.4 % of ADRs were 'definite', 52.4 % were 'probable' and 34.2 % were 'possible' in nature. WHO-UMC criteria showed 15.8 % of ADRs were 'certain', 37.8 % were 'probable' and 46.2 % were 'possible'. Of the 82 ADRs, 31.7 % were 'mild' and 68.3 % were 'moderate'. Preventability assessment showed that 34.2 % of ADRs were 'definitely preventable', 46.3 % were 'probably preventable' and 19.5 % were 'not preventable'. Also 90 % of the ADRs were Type A in nature.
Conclusions: ADRs encountered in this study were either 'definitely preventable' or 'probably preventable'. A regular mechanism to monitor the patients may be an option to minimise the ADRs.
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P010

Malnutrition as Risk Factor for Anthracyclines-Induced Cardiotoxicity in Mexican Children with Cancer

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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 and it is one of the leading causes of serious, non-cancer related morbidity and mortality in survivors [3, 4]. There are some risk factors in the literature associated with this adverse drug reaction. In Mexican children with cancer it is unknown which of them are clinically relevant.
Aim: To determine the incidence and the risk factors associated with anthracyclines-induced cardiotoxicity in Mexican children with cancer trough active Pharmacovigilance.
Method: A retrospective cohort study of children treated with anthracyclines-based chemotherapy in two pediatric hospitals from Mexico for the period from 2011 to 2015. To identify the adverse drug reactions, the active Pharmacovigilance was proposed. The causality analysis was performed by Naranjo algorithm. Cardiotoxicity was defined according to the common terminology criteria for adverse events. Relative risks were calculated with confidence intervals al 95 % (95 % CI) to determine anthracycline-induced cardiotoxicity. Multiple logistic regression was performed to identify independent risk factors.
Results: 105 pediatric patients (median age 5.8 years, range 0.2–17 years) were included in the study. Anthracycline-induced cardiotoxicity incidence was 17.1 %. Independent risk factor for anthracycline-induced chemotherapy was malnutrition at diagnosis [odds ratio (OR) = 3.39 (95 % CI (1.05–10.90)].
Conclusions: This study showed the incidence and the risk factor for anthracycline-induced chemotherapy through active Pharmacovigilance. Malnutrition at diagnosis is a significant risk factor that can be preventable by implementing nutritional support before and during treatment with anthracyclines.
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P011

The Risk of Hyperglycaemia with the Use of Rituximab in Rheumatoid Arthritis. Results from a Meta-analysis of Randomised Clinical Trials

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Introduction: Rituximab is an anti-CD20 monoclonal antibody used for a broad variety of B-cell malignancies; it has been approved for the treatment of various CD20-expressing lymphomas or leukaemias, and in rheumatoid arthritis (RA) in combination with methotrexate. The association between hyperglycaemia and the use of rituximab in patients with non-Hodgkin's lymphoma has been clearly confirmed. Hyperglycemia in patients with hematologic malignancies has been associated with poor outcomes including increased risk of infection, organ dysfunction, durability of remission, graft-versus-host disease, and mortality. This association has also been observed in animal models where rituximab induced hyperglycaemia in long-term normoglycemic human CD20 transgenic non-obese-diabetic mouse models. But, there is uncertainty about the association of hyperglycaemia with rituximab in (RA).
Objective: Our study, a systematic review and meta-analysis (SR&MA), aimed to provide reliable assessment of the risk of hyperglycaemia and rituximab use in RA.
Methods: This SR&MA was registered with PROSPERO database (CRD42014015655) as protocol for a complete evaluation of the safety profile of RTX-RA. The search strategy involved randomised clinical trials using rituximab in RA, and it was performed from January 1990 to December 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 outcomes evaluated were: the number of adverse events and hyperglycaemia reports as outcomes of interest. Analysis of odds ratio (OR) as measure of effect and 95 % confidence intervals (CI 95 %) and *p*-values as generated from the Chi-squared were calculated; heterogeneity was assessed using the I^2 test.
Results: Nine publications were selected for review involving 3272 subjects, and six publications were included in the meta-analysis, involving 2249 subjects. Two publications, with the same population, reported the outcome of hyperglycaemia (Edwards et al. and Keystone et al.). Our results for the group rituximab-alone vs placebo-methotrexate were OR 0.65, (95 % CI 1.03–4.11); $p = 0.646$, $I^2 = 0.000$; in the group rituximab-methotrexate vs placebo-methotrexate, OR 1.00, (95 % CI 0.19–5.28); $p = 1.000$, $I^2 = 0.000$; and in the group rituximab-cyclophosphamide vs placebo-methotrexate, OR 0.97, (95 % CI 0.19–5.14); $p = 0.975$, $I^2 = 0.000$. We found no evidence of association between rituximab (different subgroups) and hyperglycaemia vs placebo-methotrexate.
Conclusion: Our results suggest no evidence of association between rituximab in RA and the risk of hyperglycaemia, but the possibility of type II error is likely due to the fact that only two publications, using the same sample, reported the outcome of hyperglycaemia with a frequency between 5 and 7.5 %. Further studies are needed to confirm/reject our findings.

P012

Drug Storage and Disposal Practices in Homes of Western India

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Introduction: Drug storage at home is a risk factor in relation to irrational drug use mainly due to the easy access, and improper storage. (1) When medicines are exposed to higher temperatures, generally, their physical appearance changes, efficacy and potency reduced, drug become inactive or there may be development of adverse drug reactions (ADR). (2) Many unused medicines are disposed of through various ways including household rubbish bins which end up in landfill and may damage the environment. The amount of data available on the storage of home medication and drug disposal among the population especially in Gujarat, India is limited.
Aim: This study was aimed to know the actual picture of drug storage at homes and disposal practices of medicines.
Method: A cross sectional study was conducted in Anand district of Gujarat, India during the year 2012–2014 visiting 400 each in urban and rural houses, after Ethics Committee approval. Written consent of the participants was taken and confidentiality was maintained. The storage condition of medicine was checked by inspecting the home where medicine kept. The participant was asked about the accessibility of medicine by children or demented patients and the method of disposal of medicine they follow. The data were subjected to number, percentage and Chi-square test as applicable. P values less than 0.05 was considered as significant.
Results: A total of 3438 medicines formulations (1915 in urban and 1523 in rural area) were found in 729 of 800 houses visited. Significantly more number of medicines ($p < 0.0000$) was appropriately stored in urban area (94.78 % for place and 92.43 % for temperature) than in rural area (87.39 % each for place and temperature). A significant number of medicines had easy access by children in the rural area (1.88 % in urban and 4.40 % in the rural, $p < 0.00001$). It was observed that the major way of the disposal of medicines in the urban (60.25 %) and rural (65.75 %) areas was in the garbage. Next to it were throwing the medicines in dustbin (30.75 % in urban and 8.75 % in rural) and in open space or outside the house (2.25 and 14.75 % in urban and rural area, respectively). Advice regarding the disposal of medicines by the prescribers was given for only in 113 of 2937 medicine formulations. Though it was less but in urban area it was significantly more ($\chi^2 = 28.3967$; $P < 0.00001$).
Conclusions: Improper storage and disposal of medicines found in our study suggest the role of education on proper storage and disposal of unwanted medicines through discussion with patients or by distribution of leaflets regarding ways of disposal by health care providers especially doctors and pharmacists.
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P013

Overview of the Safety of Anti-VEGF Drugs: Data from the Italian Spontaneous Reporting System

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Introduction: Anti-VEGF drugs (pegaptanib, ranibizumab, aflibercept, bevacizumab) are widely used as intravitreal (IVT) administration for the treatment of ocular diseases (e.g. age-related macular degeneration, diabetic maculopathy) and, some of them, also for the treatment of specific cancers. The systemic use of anti-VEGF drugs in cancer treatment has been associated with an increased risk of serious adverse drug reactions (ADR), such as hypertension, stroke and myocardial infarction. If this risk is also associated with IVT administration of low doses of anti-VEGF drugs is unclear.
Aim: The aim of this study is to provide an overview of anti-VEGF drug safety using the Italian spontaneous reporting system (SRS) data.
Method: We analyzed ADR reports attributed to anti-VEGF drugs in the Italian SRS during the period January 2001–February 2016. Descriptive frequency analyses as well as signal detection (lower bound of the proportional reporting ratio (PRR $\geq$ 1) have been conducted, stratifying by indication of use.
Results: A total of 294,023 ADR reports have been collected and, of these, 2477 (0.8 %) were related to anti-VEGF drugs: 2174 (87.8 %) and 299 (12.1 %) reports were attributed to systemic and IVT use, respectively. Regarding suspected drugs, 2152 (86.7 %) reports were related to bevacizumab, 187 (7.5 %) to ranibizumab, 140 (5.6 %) to aflibercept and 4 (0.2 %) to pegaptanib. The mean age of anti-VEGF users with ocular diseases was higher than that of cancer patients (74.0 $\pm$ 10.0 vs. 62.1 $\pm$ 11.0 years) ($p = 0.033$). Serious ADRs (n = 917), including 49 fatal cases, accounted for 37.0 % of total reports. Stratifying by therapeutic indication, anti-VEGF drugs for ocular use were associated with a greater frequency of serious ADR reporting compared with that for oncology use (n = 176, 58.9 % vs. n = 739, 34.0 %) ($p < 0.05$). Among reports related to oncology use, the most frequently reported ADRs were "gastro-intestinal" (n = 673; 31.0 %), "vascular" (n = 531; 24.4 %), "hematological" (n = 374; 17.2 %) and "respiratory" (n = 323; 14.9 %) disorders. Regarding IVT use, the most frequently reported ADRs were "ocular" (n = 80; 26.8 %), "general" (n = 77; 25.8 %), "nervous system" (n = 73; 24.4 %) and "cardiac" (n = 48; 16.1 %) disorders. A statistically significant association between ischaemic stroke and ranibizumab (PRR 94.7; 95 % CI 63.1–142.2) or bevacizumab both for IVT (PRR 54.7; 26.6–112.4) and systemic use (PRR 9.5; 6.3–14.3) was observed.
Conclusions: Most ADRs attributed to anti-VEGF drugs for ophthalmologic use are systemic. In particular, reports of cardiac and nervous system ADRs associated with IVT require further investigation. In addition to the use anti-VEGF drugs in cancer treatment, also their IVT administration could yield detectable levels in the systemic circulation with the potential to increase the risk of ADRs, especially in elderly patients.

P014

Idelalisib and Progressive Multifocal Leukoencephalopathy

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Introduction: Idelalisib is a first-in-class lipid kinase inhibitor approved for use in US and in Europe for the treatment of relapsed chronic lymphocytic leukemia (CLL) and certain lymphomas in combination with rituximab in summer 2014. The licensure applications included interim results in two pivotal trials; accelerated approval pathways allowed earlier patient access to the medicine with final results of the ongoing clinical trials expected in the post marketing period. In March 2016, the marketing authorization holder halted six clinical trials using idelalisib in combination with other drugs due to a high rate of serious infections [1]. A subsequent review of a global database has identified progressive multifocal leukoencephalopathy (PML) as a potential safety concern.
Aim: To investigate a potential relationship between idelalisib and PML.
Methods: Clinical review of individual case safety reports for idelalisib identified using the MedDRA SMQ "demyelination".
Results: As of 6 April 2016 there were six cases of leukoencephalopathy included in VigiBase®; four were cases of PML. Two of the reports were "spontaneous" and four were from clinical studies. The cases arose from multiple countries: Germany, Portugal, Spain, the UK, and the US. Four were males and two were females; age range was been 56 and 77 years. In five cases, idelalisib and rituximab were both suspect agents; in one case, additional agents were also considered to be suspect. One report did not report rituximab as either past or concomitant therapy; obinutuzumb was the co-suspected medication. Time to onset ranged between 2 weeks and 6 months. Three of six cases had a fatal outcome; two cases were recovering at the time of the report.
Discussion: PML has been associated with both CLL as well as with the use of rituximab [2, 3]. Although post marketing exposure data is not publically available, given the limited trial size and time since approval, six case reports may indicate a higher incidence of occurrence than expected even taking into consideration the confounding factors of CLL and concomitant rituximab based upon previous estimations of the incidences of PML with each of these individual risks.
Conclusions: The purpose of the communication of this signal is to encourage further investigation to determine if there is an additive risk for PML with the use of idelalisib with rituximab in patients with CLL. Further risk minimization measures may be required. This signal exemplifies the role of Pharmacovigilance in the rapid access to medicines whose approval was based upon limited clinical trial data.

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P015

Adverse Drug Reactions Due to Cosmetics Notified by ADR Monitoring Centre in a Tertiary Care Hospital

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Introduction: Cosmetics are articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance [1].
Aim: Untoward reactions to cosmetics are the commonest single reason for hospital referrals with allergic contact dermatitis. In most cases, these are only mild or transient and most reactions being irritant rather than allergic in nature. Various adverse effects may occur in the form of acute toxicity, percutaneous absorption, skin irritation, eye irritation, skin sensitization and photosensitization, mutagenicity/genotoxicity. This study was conducted with an aim to assess the safety profiles and preventive strategies due to a cosmetic product.
Method: All adverse drug reaction (ADR) forms filled from June 2015 to May 2016 were scrutinized and forms with ADRs due to cosmetics were analyzed and assessed for causality, preventability and severity.
Results: Out of 300 ADR forms, 30 ADRs are due to cosmetics. 68 % patients were females and mean ± SD age was 25 ± 10 years. Rash, allergic contact dermatitis and skin irritation were the most common presentations. Most frequent culprit cosmetics included fairness cream and demelanizing agents. Majority of the patients had mild to moderate reactions and recovered completely after medical management.
Conclusions: Although, cosmetic products have rarely been associated with serious health hazards, this does not mean that cosmetics are always safe to use, especially with regard to possible long-term effects as the products may be used extensively over a large part of the human lifespan. Cosmetics and personal-care products may contain ingredients whose safety is unclear or which are known to pose health risks. ADR Monitoring Centre (AMC) under Pharmacovigilance Programme of India (PvPI), with special attention to monitoring and reporting of ADRs must be encouraged. Awareness about ADRs due to cosmetics can help in their timely detection and management, thereby restricting the associated damage.
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P016

Due Among Neonatal and Paediatrics In-Patients at a Children's Tertiary Care Hospital

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Introduction: Children are not small adults since they represent a continuous phase of rapid growth and development and therefore, drugs should be used cautiously and rationally among these age groups. There is paucity of published literature on drug utilization patterns among neonatal and paediatric patients from the state of Jammu and Kashmir, therefore this study was undertaken to generate some baseline on the subject.
Aim: Main aim of this study was to study the drug utilization patterns among neonatal and paediatric in-patients at a children's tertiary care hospital with a view to assess rational drug prescribing in the study population.
Method: A prospective, cross sectional and observational drug utilization study was conducted among neonatal and paediatric in-patients admitted to General Paediatrics Ward, Neonatology Ward, and Paediatrics Intensive Care Unit at a Srinagar based children's tertiary care hospital for a period of 6 months using WHO core drug use indicators. Index of rational drug prescribing (IRDP) was also calculated to assess rational prescribing.
Results: A total of 508 neonatal and paediatric in-patients were enrolled in the study, out of which 327 were males and 181 females. Sepsis (14.37 %) was found to be the most common disease followed by acute gastroenteritis (12.40 %), bronchopneumonia (9.4 %) and respiratory distress syndrome (8.1 %). Mean hospital stay was found to be 5.007 ± 0.111 days. A total of 2350 drugs were prescribed to all the study patients during the study period. Average no. of drugs per prescription was found to be 4.626 ± 0.098. Prescribing of the drugs by their generic names was to the extent of 62.51 %. A total of 344 (67.71 %) prescription encounters were identified with an antibiotic prescribed and a total of 474 (93.31 %) encounters were found with an injection prescribed. Index of rational drug prescribing was found to be 2.78 out of 5. A total of 105 (20.67 %) prescriptions were found to contain off-label medicines and the overall percentage of off-label medicines prescribed was found to be 5.74 %. A total of 67 drug–drug interactions were also detected.
Conclusions: Prescribing of drugs to paediatric patients in the present study was by and large found to be in accordance with national and international standards and guidelines. Polypharmacy, prescribing of antibiotics was common. Most common route of drug administration was found to be the parenteral route. Off-label and unlicensed use of medicines should be minimized and there is also a need for more paediatric clinical trials so that children receive the drug therapy which is best suited and safe for them.

P017

Interactive Pharmacovigilance Website: A Useful Tool for ADR Reports

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Introduction: The Pharmacovigilance coordination of Ile-de-France officially launched an interactive Pharmacovigilance website in June, 2014. The website design comprises two areas, one for patients and patient associations, and another for healthcare professionals (HCP) who access their area through a personal account. This website was developed to promote reporting of adverse drug reactions (ADR) in particular by patients and liberal healthcare professionals who only report a few ADRs [1].
Aim: To describe the initial results 23 months after the Pharmacovigilance website was launched.

Method: A retrospective study was carried out between June, 2014 and March, 2016 to assess and compare the characteristics of ADR reports and questions received via the website, with those received through traditional means (post, fax, email or phone) by the Paris Henri Mondor Pharmacovigilance Centre.
Results: During the study period, 288 healthcare professionals created their personal account. A total of 202 ADRs were reported, 101 (50 %) by patients or family members and 101 (50 %) by HCPs. Of these, 70 % were liberal HCPs. In the same period, 14.6 and 13.9 % of ADR reports received through traditional means were reported by patients and liberal HCPs, respectively. At national level, around 5 % of ADRs were reported by patients. Regarding the severity, 69 % of ADRs reported via the website were non-serious, versus 39 % via traditional means. We also received 102 questions through online forms, 62 (60, 7 %) from patients or family members and 40 (39.3 %) from HCPs. The number of questions received online from patients was ten times higher than that received through traditional means.
Conclusions: These results show that the website is a useful tool to improve ADR reporting rates, especially from patients and liberal HCPs. Users can report an ADR at any time and track their report. The process of online ADR reporting seems to have been accepted well, as several HCPs have reported more than one ADR. Regarding questions, the website was used more by patients than by healthcare professionals, who still seem to prefer the familiar conventional means. To pursue and increase the use of the website some actions have since been developed, such as the possibility for users to complete or edit their ADR report as often as necessary. In the future, it would be interesting to study the quality of the online ADR reports.
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P018

Adverse Events in HIV/TB Co-treatment in Kinshasa

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Introduction: Human immunodeficiency virus infection (HIV) and tuberculosis (TB) are Public Health problems in Democratic Republic of the Congo (DRC). In co-infected patients, both diseases worsen the outcomes of one another. The concomitant treatment of both diseases has proven to save lives but needs to be prompt and the patient needs to be highly compliant to achieve the objectives of treatment. Yet the co-treatment exposes to unfavourable outcomes related to overlapping of adverse events (AE) and drug interactions. On the other hand, the increase of access to treatment is a clearly defined goal of the WHO and affected countries. As a consequence, more and more patients are expected to be on co-treatment with ARVs and Anti TB drugs. There is a need to understand more about safety outcomes of this combination.
Aim: The objective of this study is to assess AE associated with co-treatment of both diseases compared to treatment of HIV alone in two health facilities previously trained in Pharmacovigilance in Kinshasa.
Method: A retrospective study was conducted in two health facilities in Kinshasa. Two groups of patients were identified: the TB/HIV group and the HIV alone group. Baseline characteristics, prevalence of AE and their severity and seriousness as well as interruption of treatment were compared in both groups. The World Health Organisation Adverse Reaction Terminology (WHO-ART) was used to classify AE and the ICH definition was used for seriousness. Data were entered in Epi-info 7, then exported in Stata 12.0 for analyses. The Wilcoxon nonparametric test or the Pearson's Chi-square test were used for comparisons.
Results: A total of 382 patients' files were eligible among which 269 in the HIV alone group and 113 in the TB/HIV group. Baseline characteristic were comparable in both groups except median weight: 52 [12–90] vs. 57 [16–105] kg ($p = 0.0225$) and CD4 cell count: 110 (1–508) CD4/mm^3 vs. 148 (1–844) CD4/mm^3 ($p = 0.0015$), which were significantly lower in the HIV-TB group. Serious AE: 16 vs. 6 % ($p = 0.0108$), treatment interruption: 9 vs. 2 %, ($p = 0.0107$) and lost to follow-up patients: 40 vs. 21 % ($p = 0.0002$) who have shown to experience bad outcomes, were more frequent in the HIV/TB group.
Conclusions: Special care and must be taken for TB/HIV patients who experience the bad effects of both diseases at initiation of treatment, experience more serious AE leading more frequently to interruption of treatment and are the most lost to follow up.
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P019

Exceptional Case of Muscle Rupture Associated with Levofloxacin

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Introduction: Levofloxacin is a broad-spectrum antimicrobial agent. It is efficacious in pulmonary and otorhinolaryngological infections and is commonly used in nosocomial infections. Its musculoskeletal side effects, as for other fluoroquinolones, are characterized by frequent tendinopathies including Achilles tendon rupture [1] and muscle affections (myalgia, muscle weakness, increased muscle enzymes) rhabdomyolysis [2]. However, muscle rupture is exceptional. We report herein a case of muscle rupture associated with levofloxacin.
Results: An 81-year-old male patient with lung emphysema was treated for an acute bronchitis with Levofloxacin 500 mg 1 tab per day, Beclomethasone 400 mcg 2 inhalations twice a day, Formeterol inhalation of a capsule every 12 h, and Dextromethorphane 30 mg orally every 8 h. Ten days later, he presented left calf pain with erythema. No notion of

trauma or significant muscular effort was mentioned at clinical history. At physical examination, palpation revealed a cord. A Doppler ultrasound of the lower limb, done for suspicion of phlebitis, revealed a subfascial detachment of the gastrocnemius muscle and a hematoma extended to the upper third of the calf. The diagnosis of muscle rupture was established. All drugs were stopped. The symptoms disappeared through rest only after about 10 days.

Conclusions: An 81-year-old male patient with lung emphysema was treated for an acute bronchitis with Levofloxacin 500 mg 1 tab per day, Beclomethasone 400 mcg 2 inhalations twice a day, Formeterol inhalation of a capsule every 12 h, and Dextromethorphane 30 mg orally every 8 h. Ten days later, he presented left calf pain with erythema. No notion of trauma or significant muscular effort was mentioned at clinical history. At physical examination, palpation revealed a cord. A Doppler ultrasound of the lower limb, done for suspicion of phlebitis, revealed a subfascial detachment of the gastrocnemius muscle and a hematoma extended to the upper third of the calf. The diagnosis of muscle rupture was established. All drugs were stopped. The symptoms disappeared through rest only after about 10 days.

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P020

Years of Pharmacovigilance in New Zealand—Lessons in Sustainability and Growth

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Introduction: The Centre for Adverse Reactions Monitoring (CARM) commenced operation as the New Zealand National ADR Monitoring Centre in April 1965. CARM is one of the very few such national monitoring centres that are not within the regulator. CARM has become entrenched as a respected service to its reporters and a source of quality ICSR case detail. For many years CARM sustained the highest rate of reporting per capita as measured by the Uppsala Monitoring Centre. CARM has often been host other smaller national centres who have been keen to learn how a mature but relatively limited resourced facility has achieved its success including its contribution and integration in research.

Aim: To reflect and elaborate on the key factors contributing to the success of a mature national Pharmacovigilance Centre.

Method: To illustrate that whilst the populating and maintenance of a Pharmacovigilance database common to all national centres remains the core activity, the synergy arising from other complementary activities and operations has been a crucial influence to success.

Results: Key success factors include: a service-related synergy in supporting clinical dialogue and queries by actively sharing relevant empirical evidence from the CARM data base; networking with closely related projects under CARM's parent umbrella grouping (NZPhvC) such as the Medication Error Reporting Programme and historically the Intensive Medicine Monitoring Programme and Intensive Vaccine Monitoring Programme; and the support and facilitation of under and post graduate research projects with CARM data. Utilisation of Pharmacovigilance infrastructure and causality assessment expertise to support emerging Public Health concerns. A patient- and reporter-centric approach has also been a longstanding focus with formal case-specific feedback to reporters; the recording of an electronic alert nationally for those ADR reports (against voluntarily-indented patient details in ICSRs) that suggest precaution or contraindication to the future use of a medicine; and operating as a single point-of-contact triaging medicine safety related concerns and facilitating appropriate connections.

Conclusions: The combined effect of synergistic and complementary activities and operational approach has been instrumental in sustaining the credibility, utility and growth of support of the NZPhvC as a national resource which has seen its role extend into areas beyond monitoring of traditional medicine-related ADRs into a broader vigilance and drug safety surveillance role. This model adds value to the relevance of Pharmacovigilance as a dynamic tool for clinical decision making, patient support and reassurance, providing richer data to inform research agendas and national drug safety initiatives.

P021

The Challenges of Traditional Medicine and Pharmacovigilance

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The influence of religious, sociocultural, and socioeconomic issues, traditional practices, and belief in the use of herbal medicines (HM) is evident, particularly in Chinese, Indian, and African societies. Documented use of HM in Western societies is also high. Until now, there are no longitudinal data for prevalence of use of HM worldwide. The market research data indicate increasing sales of licensed and unlicensed HM. This suggests that large numbers of people are using HM. The contribution made by traditional medicine to the modern system of medicine is worth noting. Indeed, some well-established drugs have been developed by scientists from plants. An example with salicylic acid, used traditionally to reduce pain and inflammation is originally a derivative from plants of the *Salix* genus and which gave rise to the synthesis of acetylsalicylic acid. As with all medicines, HM have been shown to have the potential to cause adverse effects which are related to a variety of causes, including inherent properties such as the presence of toxic constituents, adulteration, mistaken use of the wrong plant species, incorrect dosing, errors in use, and contamination. Furthermore, HM can affect pharmacokinetic and pharmacodynamic properties of conventional drugs and thus can cause herb–drug interactions. The current model of pharmacovigilance with all tools and methodologies was developed for conventional drugs. The characteristics of HM and the ways in which these products are named, sourced, and utilized constitute challenges for their Pharmacovigilance. The challenges of Pharmacovigilance and traditional medicines largely depend upon improving Pharmacovigilance systems for HM. Some of these factors will already be present in some Pharmacovigilance systems but this is not the case in the majority of member countries of the WHO international Pharmacovigilance program. These challenges can be shown in seven distinct points that will be discussed point by point in order to highlight the challenges of traditional medicine and Pharmacovigilance:

1. Safety, efficacy and quality of herbal medicines
2. Herbal medicines regulatory framework

3. Herb–drug interactions
4. Patient categories
5. Awareness
6. Communication and education
7. Scientific research

P022

Impact of Different Reporting Procedures of AEFIs by Elderly

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Introduction: Between September 2014 and February 2015, the Netherlands Pharmacovigilance Centre Lareb received an unexpected high number of reports of Adverse Events Following Immunization (AEFIs) following administration of a pneumococcal polysaccharide conjugated 13-valent adsorbed vaccine (Pneu-13) of elderly. The reports came from a selected group of 21,000 people of 70 years or above, who participated as controls in the CAPiTA study [1, 2]. After unblinding these controls were offered a Pneu-13 vaccination. Following vaccination they received a leaflet with information about the importance of reporting AEFIs. In addition, they were offered to report by phone, instead of reporting via an online form only.
Aim: Primary aim of this study is to evaluate differences in number and characteristics of reports of elderly, who received additional information about reporting AEFIs compared to the routine procedures during the annual influenza campaign, were the aforementioned information is not provided. The secondary aim of this study is to investigate the preference of these elderly in terms of reporting AEFIs by phone or by means of an online form.
Method: Comparison of the number of reports and characteristics of reports after Pneu-13 vaccination with reports of vaccinees of 70 years or above after influenza vaccination. A telephone survey was conducted on awareness of different possibilities of reporting AEFIs and personal preference of reporting.
Results: Lareb received 390 spontaneous reports after Pneu-13 vaccination out of 21,000 vaccinees (1.9 %), of which 70.7 % reports of women. 1.3 % Reports were serious, 96.7 % reports of consumers. Of the latter group, the proportion of reporting by phone was 73.8 %. Between October 2014 and March 2015 Lareb received 44 spontaneous reports out 1.2 million elderly aged 70 years and above after influenza vaccination (0.004 %), of which 59.1 % reports of women; 9.1 % serious reports and 70.5 % reports were from consumers. The proportion of reporting by phone in the latter group was 10.7 %. Twenty-five reporters were interviewed. Of the interviewees eight has no internet access and five started electronic reporting, but did not succeed completing the form. 21 interviewees (84 %) has a preference of reporting by phone.
Conclusions: Compared to the number of reports after influenza vaccination, the number of reports after the Pneu-13 vaccination where people were actively invited to report, is relatively high, but it mainly concerned non-serious reports. Providing a leaflet after vaccination, may encourage elderly to report AEFIs. In addition, our findings suggest that offering elderly the opportunity to report by telephone, this may encourage reporting.

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P023

Approaches to Overcome the Challenges in Running Pv Programs by Involving Stakeholders at Different Levels

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Introduction: The present ADR monitoring system is largely depends on "spontaneous reporting", which offers a high underreporting rate. This underreporting of ADRs by healthcare professionals has been identified as a serious drawback of the voluntary reporting system, failure to calculate the incidence rate and uncertainty in causality judgment. Even the quality of some ADR reports does not meet the requirements of analysis and evaluation. Some reporting lacks clear description, low data standardization and even the contents of reports mostly focus on known and common reactions. The Pharmacovigilance programme in developing countries is facing other difficulties due to various other reasons. Practices and promotion of complementary and alternative medicine (CAM) is major issue in reporting ADRs. Several preparations containing allopathic drugs are sold as herbal medicines, while some drugs are sold without prescriptions (OTC) and taken as self-medication because of commercial advertising; hence it is difficult to trace the use of these medicines.
Aim: The present study is aimed to offer an analytical study of current problems and solutions of Pharmacovigilance programme. The necessity of implementation of appropriate Pharmacovigilance, its requirements, problems, limitation and the process how it can further be improved have been emphasized.
Method: Literature review.
Results: The author of the present paper would discuss different approaches to overcome the challenges in running Pharmacovigilance programme involving stakeholders at different levels including drug regulatory authorities, ADR monitoring committees, hospital administration, health professionals, consumers, etc.
Conclusions: ADR monitoring information network has achieved ADR reporting capabilities, but failed to fully accomplish an automatic warning and assessment system. There is still a lot of work to do in the research and exploration of improved ADR monitoring.

P024

Impact of Integrating Pharmacovigilance in Moroccan Tuberculosis Control Programme

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Introduction: Public Health programs are well structured but often represent a favorable model for the development of adverse events (AEs) by irrational use of drugs.

Aim: The objective of this work is to demonstrate the interest of integrating Pharmacovigilance in Moroccan Tuberculosis Control Programme (MTCP).
Method: Integration of Pharmacovigilance in MTCP was conducted in October 2012 with the Global Fund Support. Using spontaneous reporting after Pharmacovigilance sensitization sessions. Comparison of spontaneous reports before and after the integration of Pharmacovigilance in MTCP (January 2010–October 2012/October 2012–April 2013) using SPSS Version 10.0 for data analysis. Detection of Moroccan signals using the information component (IC) of VigiMine. Development of actions risk minimization.
Results: As reports indicators: the average number of spontaneous reports increased from 3.6 to 37.4 cases/month (10.3 times, $p < 10^{-3}$). As AEs indicators: the average age was 40.7 ± 17.5 years, the sex ratio was 0.8. Hepatic reactions (32.7 %) predominated during the first period while skin reactions (22.7 %) were in second period ($p = 10^{-4}$), 40.9 % of cases in the first period were serious against 23.5 % in second period (p = 0.003), 4.7 % of cases in the first period have been fatal against 0.7 % in second period ($p < 10^{-4}$). Five signals were generated (hepatic enzyme increase IC = 2.77, arthralgia IC = 2.64, pruritus IC = 1.84, acne IC = 1.54, hepatitis IC = 1.22). As action of risk minimization, a national procedure of TB hepatotoxicity was developed.
Conclusions: The integration of Pharmacovigilance in Moroccan Tuberculosis Control Programme allowed rapid identification of events that are likely to affect adherence to treatment and determination new signals of antituberculosis drugs.
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P025

Pharmacovigilance in HIV/AIDS Public Program Health: Moroccan Experience

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Introduction: In Morocco, if Pharmacovigilance system and HIV/AIDS Public health program (Programme National de Lute Contre Le Sida: PNLS) are considered to be well structured and efficient, integration of Pharmacovigilance in the PNLS is just beginning. To this effect, close collaboration has been initiated between the Centre Antipoison et de Pharmacovigilance du Maroc (CAPM), recognized in 2012 as a WHO Collaborating Center, and the Epidemiology and fight against diseases Direction (Direction de l'épidémiologie et de lute contre les maladies: DELM) which is the structure of the Ministry of Health responsible for the implementation, management and proper functioning of the HIV/AIDS Public health program.
Aim: The aim of our work is to establish the safety profile of antiretroviral drugs used in AIDS program among the Moroccan population and to detect and analyse potential Pharmacovigilance signals.
Method: We have proceeded to an analyse of our national Pharmacovigilance database by selecting all individual safety case report recorded with Antiretroviral drugs and comparing pre-integration and post-integration periods.
Results: 377 cases were collected; average age is 44 years the sex ration F/M is 1.55 non-nucleoside reverse transcriptase is the most complained therapeutic family with a percentage of 68.2 % followed by combination drug for HIV treatment 59.2 %, disorders Nutritional and metabolic are the most reported adverse events with a rate of 19.6 % followed by skin disorders 18.6 % medication errors and therapeutiques failures come in third place with a rate of 16.7 % then come hematological disorders 11.1 % and disorders psychiatric 10.6 %; 93 % of registered cases have been recorded that after the integration of Pharmacovigilance in the HIV/AIDS program; 350 cases in post integration period versus 27 cases in the pre integration of Pharmacovigilance period.
Conclusions: Implementing and/or strengthening Pharmacovigilance systems in resource-constrained countries is a very big challenge that all the stakeholders may held, particularly at this time when new approaches such as 'Test and Treat' are being implemented, and antiretroviral drugs are being considered for prevention of HIV transmission. Attention to drug quality and drug safety is obligatory conditions for long-term program sustainability and providing a good guarantee for patient safety. Therefore, collaborative partnership between industry, physicians, public health programs actors and national health authorities can potentially is of major importance.
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P026

Incorporation of Pharmacovigilance in Curriculum: To Whom and How Far?

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Introduction: In India, adverse drug events are not properly reported due to lack of time, low motivation, ignorance. Lack of continuing medical education on Pharmacovigilance and dearth of drug information particularly at the level of primary health centres and private practitioners lead to underreporting of ADR. The mission to safeguard the health is achievable by incorporating changes like making Pharmacovigilance reporting mandatory at all levels, introducing Pharmacovigilance inspections. The practice of self-medication and use of traditional medicines pose additional challenges as adverse events in such cases often go unreported. In

addition, there are lacunae like lack of communication among healthcare professionals, shortage of trained personnel and inadequate training on Pharmacovigilance at undergraduate level.
Aim: In order to address the challenges, one of the important steps is to incorporate Pharmacovigilance in medical and paramedical curricula.
Method: Intensive training should be given on all aspects of Pharmacovigilance to various stake holders including the patients, efficient system of communication, creating a clinical trial database for serious adverse events (SAE) and ADRs for signal detection and access to relevant data for various stakeholders. Various types of teaching and assessment modules are to be developed according to the course and job responsibilities starting from doctors, nurses, pharmacists.
Conclusions: It should be mandatory to incorporate Pharmacovigilance in medical and various paramedical curricula in order to achieve a successful outcome in proper implementation and compliance of the programme.

P027

Proton Pump Inhibitors: Real Indication or Trivialized Prescription?

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Introduction: Protons pump inhibitors (PPIs) are one of the most frequently prescribed classes of drug in the world. Yet studies consistently show that PPIs are being overprescribed in both primary and secondary care [1].
Aim: The aim of our study was to determine the rate of exposure to PPIs in old patients and to assess the appropriateness of their prescription according to French guidelines.
Method: We performed a descriptive study from 1 June to 30 August 2016 including all patients admitted in the Department of Geriatric Post Emergency of University Hospital of Toulouse with a prescription of PPI. Data concerning age, name of PPI, dose, indication, and duration of prescription and the modification of PPI prescription were collected.
Results: Among 375 patients admitted during this period, 134 (35.7) were exposed to PPIs with a mean age of 85.9 ± 6.6 years. About one third of them were exposed to PPI more than 1 year (n = 49). Prescription was inappropriate for the criteria "dose and indication" and "duration" for respectively 59 (44.0 %) and 15 (11.2 %) cases. In 50 cases (37.3 %), the PPI was renewed, stopped in 69 cases (51.5 %) and the dose was reduced for 15 patients (11.2 %).
Conclusions: According to our data, the prescription of PPI was no appropriate in about 40 % of included patients. A reassessment of their prescription with awareness of patients should be necessary to improve the Good Utilization of these "popular" drugs and to prevent some serious adverse reactions after long exposure such as acute interstitial nephritis [2] or dementia [3].
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P028

An Unexpected Long Time to Onset of Injection Site Reactions After Pneumokokken-13 Vaccine in Elderly

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Introduction: Between September 2014 and February 2015, the Netherlands Pharmacovigilance Centre Lareb received a high number of reports of Adverse Events Following Immunization (AEFIs) following administration of a pneumococcal polysaccharide conjugated 13-valent adsorbed vaccine (Pneu-13), mainly reports of injection site reactions with an unexpected time to onset (TTO) of 4–7 days. The reports came from a selected group of 21,000 people of 70 years or above, who participated as controls in the CAPiTA study [1, 2]. After unblinding controls were offered a Pneu-13 vaccination.
Aim: The aim of this study is to evaluate differences in the number of AEFIs of injection site reactions in elderly and their characteristics like TTO after Pneu-13 vaccination, compared with reports of AEFIs following seasonal influenza vaccination in the same age group.
Method: Reports of injection site reactions after Pneu-13 vaccination received between September 2014 and February 2015 were compared to reports of injection site reactions of elderly of 70 years or above vaccinated during the annual influenza campaign. Given the limited reports of elderly after influenza vaccination, reports of 5 consecutive years were selected.
Results: Lareb received 390 reports after Pneu-13 vaccination concerning 616 AEFIs of which 296 injection site reactions (47.7 %). Injection site reactions with a TTO >2 days were reported 176 times (58.4 %), mostly 4–7 days. In the group of elderly 80 years or above these reactions were reported more often compared with elderly of 70–80 years; i.e. 69.0 vs. 53.8 % (crude OR 1.9, 95 % CI: 1.12–3.24). Between October 1, 2010 and May 1, 2014 Lareb received 136 spontaneous reports concerning 240 AEFIs after influenza vaccination, of which 46 injection site reactions (19.2 %). The proportion of injection site reactions with a TTO >2 days was 6.6 %.
Conclusions: Even though the vaccines itself are not completely comparable, reports after Pneu-13 vaccination of elderly aged 70 and above, the proportion of AEFIs of injection site reactions after Pneu-13 vaccination compared with influenza vaccination was relatively high. The proportion of reports of injection site reactions with a TTO >2 days was more outspoken in the Pneu-13 group as compared to the influenza group. Especially in elderly of 80 years this long TTO was more outspoken. Our findings indicate a possible increased risk for injection site reactions with a long TTO with increasing age after vaccination with pneumococcal polysaccharide conjugated 13-valent adsorbed vaccine.

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P029

Onset Time of Adverse Events to Nifurtimox–Eflornithine Combination Therapy: Review of Reports

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Introduction: Human African trypanosomiasis (HAT) is a neglected tropical disease considered as lethal without treatment. Nifurtimox-Eflornithjine Combination Therapy (NECT) is recommended by the national program of HAT control. Patient's adherence may be influenced by the adverse drug events (ADE) occurrence. Then, there is a need to monitor ADE in order to improve the outcome of the treatment.
Aim: To analyze adverse events (AE) profile of NECT and determine their time of occurrence.
Method: Adverse events related to NECT, introduced in the Uppsala Monitoring Centre's database (VigibaseTM) from January 2010 and January 2016, were retrieved. Causality assessment of reports was done according to the WHO method. Only reports with at least "possible" grading were analyzed. International conference of harmonization criteria applied to assess seriousness.
Results: A total of 678 individual reports were retrieved and 2891 AE were accounted. 1.9 % of these were classified as serious. Gastro-intestinal (42 %), Body as a whole—general (22.2 %) and central and peripheral nervous disorders (16, 7 %) were the commonest system affected. Median onset time was 4 days (IQR: 1–15 days). Half (1423/2891) of AE occurred between 1 and 3 days of treatment. Clinical signs were reduced on the fourth day. Between 4th and 7th day, number of case of psychiatric AE increased. We note also three cases of fungal infection. From 10th day and more, period corresponding to treatment discontinuation, some AE especially psychiatric, nervous and gastrointestinal system disorders (54/2891) persist. One case of anaemia has been reported in 14th day after treatment starting.
Conclusions: This study has highlighted, to some extent that AE of NECT overlap with clinical manifestations of trypanosomiasis. Data on chronology of AE related to NECT, may improve medical care of patient with trypanosomiasis.
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P030

Adverse Drug Reactions Monitoring in Public Hospitals Using Patient Safety Network System

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Introduction: Reporting adverse drug reactions (ADRs) significantly Importance for public health. Various systems are available for ADRs reporting among different health care institutions. Voluntary ADRs reporting systems remains most valuable source of information to monitor and assess drugs reactions and adverse events [1]. Majority of ADRs are preventable through improved health professions education and prescribing monitoring [2]. Many hospitals had undergone joint Commission International (JCI) accreditation which emphasizes ADR reporting under Patient safety Network (PSN) system that is linked to the database of global patient network.
Aim: This study examined the extent and incidents of voluntary ADRs reporting by health professionals in Abu Dhabi Government health care facilities that are JCI accredited and utilizing patient safety network (PSN) system.
Method: The study covered all public hospitals in the Emirate of Abu Dhabi, UAE which operated by Abu Dhabi Healthcare company SEHA. Reporting ADRs via PAN became mandatory by (JCI) which was obtained by all SEHA facilities. This study looked at 7 pharmacy departments that served 12 hospitals. A multidisciplinary Taskforce responsible for collecting ADRs, assessing causality and evaluating reactions outcomes was established. The Taskforce then forwarded the recommendations to SEHA headquarters central medication safety committee for required action. The central medication safety committee further evaluated and monitored the trend of ADR occurrence and implemented measures to improve patient safety and rationalize the use of medicines.
Results: During the period of January 2015 to March 2016, there were 309 ADR cases reported in SEHA's hospitals. Antibacterial medications were the highest category involved in ADR reporting (n = 113, 36.57 %), followed by anticancer (n = 48, 15.5 %), medicines used for iron deficiency treatment (n = 26, 8.4 %), non-steroidal anti-inflammatory drugs NSAIDs (n = 17, 5.5 %), Opioid pain medications (n = 10, 3.2 %) and vaccines (n = 10, 3.3 %). Nurses were highest in reporting ADR cases (n = 180, 58.3 %), followed by pharmacists (n = 30, 9.7 %) and physician (n = 25, 8.1 %). Data generated in the study shown low reporting rate among healthcare professionals compared to the size of the hospitals and numbers of patients experienced medication therapy [2,3]. That can be explained by the fact that it is not mandatory to report every ADR to drug use despite mandatory implementation of PAN system. Moreover many incomplete ADR reports were noticeable. Further education and awareness of the system is important to encourage reporting and detection of ADRs for improving the quality of patient care.
Conclusions: Voluntary reporting by health professionals considered the keystone in detection and management of ADRs. It is important to incorporate ADR reporting and patient safety features in database that used within accredited hospitals and encourage reporting among different groups of healthcare professionals [4].
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P031

Medicines for Women in India: What are the Key Local Issues?

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Introduction: Inequalities in gender are present globally. In India men have greater cultural rights to autonomy, social freedom, and mobility outside the home than women. Women's health needs are numerous-nutrition, general morbidity, reproductive health, disability, mental health, occupational health, and are interrelated. Discriminatory practices are prevailing against female in seeking healthcare in India. Women in India are vulnerable in terms of their health and healthcare seeking behaviour throughout the life cycle, childhood, adolescence, middle age and old age.
Aim: Several studies have shown differences in health care utilization for girls, medical attention being sought less frequently and at a later stage of illness. Indian girls younger than five have higher mortality than boys. Three common health problems affecting women are anaemia, reproductive tract infections, and depressive disorders. Anemia is common for women in India with prevalence estimated to be as high as 40–60 %. Cancer is another challenge with more than 200 women dying daily due to cervical cancer, but only 10–20 percent of Indian women in rural areas know about it.
Results: The 'key local issues' are addressing women belonging to rural India, the poor, the lower castes (especially the Scheduled Castes), the Scheduled Tribes, the less developed states and regions of India. Women belonging to any of above factors show poor health status and restricted access to healthcare. Further, with the considerable weakening of the public healthcare system and the gradual entrenchment of the market economy, differentials among socio-economic groups are widening. Few policy recommendations for these issues are—adoption of comprehensive and gender sensitive primary healthcare, strengthening of public healthcare, regulating the private sector, making the health systems gender sensitive, instituting community health insurance and strengthening of civil society initiatives.
Conclusions: The message of gender equality has not percolated deep enough to reach the family and community levels. Thus, a girl child begins her formative years on a weak foundation, and this continues all through her life. It is even transmitted to the next generation. To break this vicious circle, an urgent action-oriented behavioural change campaign, involving health, education and other social sectors, is required. However, to realize gender equity, a strong social and political will is needed.

P032

The Impact of Database Restriction on Pharmacovigilance Signal Detection of Selected Cancer Therapies

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Introduction: Disproportionality analysis in pharmacovigilance entails a large number of analytical choices [1], including database background [2]. These would be expected to result in changed signal/noise ratios, sometimes favorably and sometimes unfavorably. Restricting the database to specific subsets more reflective of background diseases may improve noise/noise ratios [3], but may be associated with an unacceptable loss of signals depending on the nature of the restriction. Pharmacovigilance signal detection in oncology is not straightforward for numerous reasons [4] including polydrug regimens, complex patient histories that result in confounding and effect modification (i.e. drug–disease interactions) and unique benefit/risk considerations resulting in higher thresholds for recognizing/reporting adverse drug events (ADEs). New drugs involving novel mechanisms may present difficult to anticipate/rationalize ADEs.
Aim: To explore the effect of an oncology drug restriction (i.e. analyzing the subset of the database consisting only of oncology drugs) on the performance of a data mining analysis using a defined reference set of oncology drug–event pairs.
Methods: We used the FAERS database. Positive control (PC) drug-medical concept (MC) pairs were selected from safety information not included in the product's first label but subsequently added as label changes [5]. These MCs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) used in FAERS to code adverse events. Negative controls (NC) were MCs with circumscribed PTs not in the corresponding Unites States Package Insert. We calculated shrinkage-adjusted observed-to-expected reporting frequencies for the aforementioned drug–PT pairs. We formulated an adjudication framework to calculate performance at the MC level. Performance metrics [sensitivity, specificity, positive and negative predictive value (PPV, NPV), signal/noise (S/N), F and Matthews correlation coefficient (MCC)] were calculated.
Results: The PC reference set consisted of 11 drugs, 487 PTs, 27 MCs, 37 Drug-MC combinations and 638 drug–event combinations (DECs). The NC reference set consisted of 11 drugs, 9 PTs, 5 MCs, 40 Drug-MC combinations and 67 DECs. Most drug-event pairs were not highlighted by either analysis. A small percentage of signals of disproportionate reporting were lost, more noise than signal; little or no gains. Specificity, PPV, NPV, F and MCC improved or showed no visible change while sensitivity declined substantially. Overall S/N improved.
Conclusion: Oncology drug restriction substantially improved the S/N ratio, but with significant credible signal loss. Without broader experience and a calculus of costs and utilities of correct versus incorrect classifications in oncology pharmacovigilance such restricted analyses should be optional rather than a default analysis.
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P033

An Exploratory Factor Analysis of the Spontaneous Reporting of Severe Cutaneous Adverse Reactions (SCARs)

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Introduction: Severe cutaneous adverse reactions (SCARs) are of prominent concern in Pharmacovigilance. They have some broad commonalities such as non-immediate nature and T-cell mediation and rare overlap syndromes have been documented, most commonly involving AGEP and DRESS, and DRESS and TEN. However they display diverse clinical phenotypes and variations in the specific T-cell immune response profile, as well as some specific genotype-phenotype associations. A natural question is the extent, if any, that the confirmed occurrence of a given SCAR with a given drug should be considered supportive of that drug causing other SCARs. If the extrapolation is sound we might expect significant inter-correlations between SCARS with respect to overall drug reporting patterns. SCARs with significant inter-correlations may reflect a unified underlying concept.
Aim: To use exploratory factor analysis (EFA) applied to an extract of the United States Food and Drug Administration Adverse Event Data base (FAERs) to assess reporting inter-correlations between a set of six SCARs (AGEP, DRESS, EM, SJS, TEN) in a geometric space defined by drug-specific reporting dimensions.
Method: We screened the data using visual inspection of scatterplot matrices for potentially problematic data patterns (e.g. U-shaped distributions) and extreme skew. We screened factorability via Bartlett's test of sphericity, KMO statistics, initial estimates of communality and the anti-image correlation matrix. We extracted factors via principle axis factoring. The number of factors was determined by Scree plot/Kaiser's rule. Because of tendency to under factor using these methods we also examined the solution with an additional factor. We examined results subject to various types of oblique rotation. We assessed the strength of the solution by the percentage of variance explained, minimum number of factors loading per major factor, the magnitude of the communalities, loadings and cross-loadings, and the reproduced and residual correlations.
Results: The spontaneous reporting data for SCARs were generally adequate for factor analysis but the amount of variance explained, shared variance, and communalities were low. These basic negative finding are a caution against extrapolating causality between SCARs. Consistent with clinical expectations, SJS and TEN did display the most shared variance. AGEP and DRESS, the other SCAR pair most often observed in overlap syndromes demonstrated modest shared variance, along with MPR. DRESS and TEN, another of the more commonly diagnosed pairs in rare overlap syndromes, did not. EM was not correlated with SJS and TEN, which likely reflects higher potential for confounding by infectious treatment indications. Other pairs of SCARS were not correlated.
Conclusions: The notion that causality of a drug for one SCAR bolsters support for causality of same drug with other SCARs was generally not supported. The one pair of highly correlated SCARs, SJS and TEN, is consistent with clinical expectations.

P034

Teratovigilance Activities in Morocco (2000–2015)

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Introduction: Teratovigilance (TRV) is the monitoring of potential risks due to health products intake during pregnancy. It improves the ratio «profit/risk» avoiding abnormalities development and abusive abortions.
Aim: The aim of our study was to describe the National TRV system (SNTV) and to perform a retrospective analysis of all data collected from 2000 to 2015.
Method: We have proceeded to a retrospective analysis of all data concerning health products exposure in pregnant women during recorded in our center from 2000 to 2015.
Results: The unit of TRV has documented 869 cases related to the use of health products by pregnant, 34.4 % were related to adverse events in Tératovigilance (NET) and 65.6 % related to requests for information (DI). Electronic way represented the predominant means of reporting of NET (65.2 %). Health professionals represented the main notifiers (79.9 %). The most incriminated health products were drugs and plants. More than 2/3 of NET are developmental abnormalities, these were mostly hydrocephalus, cleft lip/palate, spinabifida and anencephaly. The analysis of NET has detected the signal of Neural tube defects due to fenugreek. This signal was the subject of studies and lead to risk minimization actions.
Conclusions: Our study reflects the need to promote the notifications nearby health professionals and the public, and to establish the national Registry of Malformations. The network Teratovigilance play a crucial role in maintaining the momentum vigilance in pregnant and breastfeeding women.
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P035

Polycystic Ovarian Syndrome and Berberine: Safety Profile and Current Perspective

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Introduction: Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrinopathy [1], characterized by anovulation, infertility, hyperandrogenism along with hyperinsulinaemia and insulin resistance [2].
Aim: Due to a wide variability of presentations, women with PCOS may consult different health care professionals including gynecologists, endocrinologists, dermatologists, etc. Therefore, symptoms are often treated in isolation, rather than being treated as interlinked manifestations of this complex endocrine and metabolic medical syndrome. Currently, there exists no medical treatment that addresses all clinical presentations of PCOS.
Method: The present paper reviewed the safety and efficacy of off label use of Berberine as an effective phytotherapy in the management of PCOS.
Results: Berberine is an isoquinoline quaternary alkaloid isolated from many kinds of medicinal plants. The fundamental mechanism of action underlying berberine is its action on the adenosine monophosphate activated protein kinase (AMPK) [3]. This enzyme acts as the central energy regulatory control switch regulating how energy is produced and used in the body [4]. Though it's use is not associated with any serious side effects, cramping, diarrhea are the major side effects due to poor absorption of Berberine and multiple dosing instead of single oral dose prevents the above mentioned ADRs.
Conclusions: Off label use of Berberine as phytotherapy in the management of PCOS was found common amongst the practitioners of gynecologists, endocrinologists and dermatologists. The medicine was promoted as safe that could be used to treat all clinical manifestations of PCOS.
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P036

Risk factors of Ferric Carboxymaltose and Iron Sucrose in Women with Iron Deficiency Anaemia

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Introduction: Iron deficiency anaemia (IDA) is common in women and its rate is higher in India as compared to any other developing country. It is estimated that one in every two women in India is suffering with iron deficiency anaemia. In women, anaemia consequences affect the productive as well as reproductive abilities which primarily results in poor work capacity, decreased energy, diminished quality of life, fatigue or even infertility.
Aim: To compare the safety of two intravenous preparations, ferric carboxymaltose and iron sucrose, in treating the iron deficiency anaemia in women.
Method: 200 patients of Obstetrics and Gynaecology, SKIMS Medical College and Hospital, Srinagar, India with iron deficiency anemia were enrolled for the retrospective study. Patients were either treated with ferric carboxymaltose or iron sucrose. Follow up was done at week 2 and 4. Adverse drug reactions were documented.
Results: The results showed that both drugs were effective in treating the iron deficiency anaemia, but the safety profile differs. 6 % adverse drug reactions were observed in Iron sucrose and 1 % percent in ferric carboxymaltose. The ADRs reported were mild in both cases.
Conclusions: Both ferric carboxymaltose and iron sucrose are safe in treating IDA, but ferric carboxymaltose has a better compliance. The ADRs associated with ferric carboxymaltose are less when compared to iron sucrose.
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P037

Health Risks of Unknown Medicines: Evidence from Adverse Drug Reactions in Laos

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Introduction: Although important to take preventive measures towards drug-related morbidity reduction, drug safety research is impaired by the lack of knowledge of medicines used by patients. The danger of medicines of unknown identity (MUIs) (not sold in their original packaging and without written identity) has been suspected in previous studies in low- and middle-income countries of South-East Asia.

Aim: Using visual and analytical tools to identify MUIs, we designed a cross-sectional study to evaluate the incidence of and factors associated to adverse drug reaction (ADR)-related hospitalizations in adults in a Laotian central hospital in Vientiane Capital.

Method: All unplanned admissions (≥24 h) in Mahosot hospital except for acute trauma were prospectively recorded during 7 weeks in 2013, corresponding to 453 patients included. MUIs suspected to be involved in ADR(s) were identified through comparison of visual characteristics of tablets/capsules to that of reference medicines, and by nuclear magnetic resonance (NMR)/mass spectrometry (MS) analysis. Factors associated to ADR-related hospitalizations were identified by multivariate logistic regression.

Results: The incidence of hospitalization related to an ADR was 5.1 % (95 % CI 3.1–7.1) during the study period. Patients having used MUI(s) were more likely to be hospitalized because of an ADR [adjusted odds-ratio = 4.5 (95 % CI 1.7–11.5)] than patients using medicines of known identity, irrespectively of the age and gender. Gastro-duodenal bleeding ulcers were the most common ADRs (n = 9), almost half related to MUI(s). MUI(s) were more often procured in private clinics than medicines of known identity (48.4 vs. 9.0 %, $p < 0.001$).

Conclusions: Using MUI(s) increases the risk of developing ADR-related hospitalizations. In serious cases of ADRs leading to hospitalization, the absence of knowledge of medicines used by patients impairs patients' care, especially for forthcoming prescription of medicines. This study highlights the need to ensure appropriate labeling of medicines at dispensing and also to provide tools to identify MUIs in clinical settings.

P038

Use of Routinely Collected Pharmacovigilance Data in Detecting Product Quality Problems: The Ethiopia

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Introduction: Pre-marketing drug safety data is often limited, so there is a heavy reliance on Pharmacovigilance systems, particularly on spontaneous reporting of adverse drug events (ADEs). In many countries, information collected through existing spontaneous reporting systems to track product quality is either nonexistent or is underutilized. In Ethiopia, an ADE reporting tool was modified to incorporate product defects into the national ADE reporting system to allow tracing of medicines with quality problems.

Aim: This abstract describes the impact of the comprehensive ADE reporting system in identifying poor quality medicines and supporting regulatory decision making.

Method: The ADE reporting guideline and form was revised to incorporate medication error and product defects, in addition to ADEs. Also, a Pharmacovigilance forum was established to review ADE reports on suspected product quality. The forum members were selected from product registration, facility inspection, and quality control directorates. When a product quality defect report is received, the forum assigns facility inspection directorate to inspect the facility and collect samples; the quality control directorate conducts the necessary laboratory tests. The findings of the two directorates are presented and discussed at this forum. Based on the forum's recommendations, Ethiopia's regulatory authority (FMHACA) makes regulatory decisions.

Results: The yearly number of ADE reports has increased from 79 in 2012 to 411 in 2015. Of the 1112 total reports received through April 2016, 176 were related to suspected product quality issues. Of the reported quality problems, 48.9 % had visual/physical changes; 23.9 % had unexpected effects; and 23.3 % had packaging problem. Further follow-up and investigation on these products resulted in recall of 18 products, temporary closure of one manufacturing facility, suspension of a market authorization license, and permanent cessation of production for one product. In the year 2016 alone, analysis of ADE reports received by the Pharmacovigilance center resulted in regulatory measures on five products.

Conclusions: Including product quality defect in the ADE reporting tool is an effective way of identifying poor-quality products. Creating an effective platform for coordination and information sharing between different functional units of regulatory authority, for analysis, interpretation, and use of Pharmacovigilance data, is a major factor for evidence-based decision making that ensure public health safety. This system could be used to effectively identify counterfeit and substandard medicines in countries with limited capacity to undertake regular post-marketing quality surveillance.

P039

Challenges of Pharmacovigilance in the Neonate

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Introduction: Exposure to drugs during pregnancy has the potential of harming the offspring. Teratogenic effects are the most feared adverse outcomes in newborns [1]. However, a wide spectrum of less known, usually reversible and often acute, neonatal adverse events can also occur due to drug intake by mothers during pregnancy, particularly in close proximity of the delivery. These effects have been ascribed to withdrawal effects or to a residual toxicity of the drug [2].
Aim: This narrative review is aimed at the description of drugs and drug classes for which a licit maternal use in the pre-delivery period has been associated with neonatal non-teratogenic disorders, consistent with drug withdrawal or pharmacological residual effects.
Method: English-language literature indexed in MEDLINE was explored without limits of time up to December 31st, 2015. Since there is no standard clinical definition for neonatal syndromes, articles dealing with neonatal behavioural and neurological alterations after exposure to any drug were used to generate clusters of symptoms. Teratogenic effects, congenital malformations, miscarriage, stillbirth, low birth weight, and abortion were excluded.
Results: Although neonatal syndromes have been described mainly for substances used illicitly for recreational purposes, several prescription drugs have been also involved. These include mainly psychotropic medications such as opioids, antidepressants, antiepileptics (AEDs) and antipsychotics [3–5]. These effects have been sometimes explained by neonatal abstinence syndrome (NAS) caused by delivery-related discontinuation of drug disposition from mother to foetus, with symptoms that may include feeding disorders, tremors, irritability, hypotonia/hypertonia, vomiting, persistent crying and seizures, occurring since few hours from delivery up to 1 month [6]. Otherwise, neonatal neurological and behavioural effects can be caused by residual pharmacological effects resulting from drug accumulation in the newborn blood and tissues, with consequent symptoms related to the toxic effects (i.e. methadone-induced QT interval prolongation, anticholinergic effects or serotonin-like symptoms to antidepressants, floppy syndrome to benzodiazepines), usually developing few hours after birth.
Conclusions: These effects are mostly mild, even though severe reactions, rarely fatal in nature, may occur and their early recognition and management can be helpful in reducing their clinical impact on newborns. With few exceptions, validated protocols for the assessment and management of NAS or residual pharmacological effects in neonates are often lacking or incomplete. Spontaneous reporting of these adverse reactions seems limited, although it might represent a useful tool for improving our knowledge about drug-induced neonatal syndromes.
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P040

Drug Utilization Evaluation as a Tool for Minimizing Risk and Promoting Rational Use of Medicines

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Introduction: Drug utilization research is defined as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences. These studies are carried out to evaluate whether the drugs are prescribed, dispensed and used appropriately, in tune with established guidelines with a view to minimize risk and improve patient's therapeutic outcomes.
Aim: Six drug utilization evaluation studies were conducted over the past 5 years with an aim of assessing the prescribing patterns of doctors and utilization patterns of patients in Kashmiri population.
Method: An overview of the results of six drug utilization studies carried out over the past 5 years including drug utilization evaluation of statins in patients of diabetes mellitus at a tertiary care hospital; Evaluation of the prescribing patterns of anti-hypertensive drugs in patients of hypertension with associated co-morbidities at a tertiary care hospital; Drug utilization patterns and risk assessment for primary and secondary prevention of cardiovascular disease at a tertiary care hospital, Drug utilization patterns and risk assessment for renal impairment patients at a tertiary care hospital and Drug utilization evaluation among paediatric and respiratory medicine patients shall be presented.
Results: By and large drugs were prescribed in accordance with established guidelines though there is scope for improvement. An overview of results pertaining to physicians' adherence to standard guidelines; level of adherence to WHO Core and Complementary Drug Use Indicators; cost-effectiveness of some of the prescribed medicines; patient adherence to the prescribed medications using Morisky scale and the percentage of drugs prescribed out of Essential Medicines List shall be presented.
Conclusions: Drug utilization research can facilitate safe, effective and rational use of drugs in the community. With the completion of these studies a baseline of vital information and evidence shall be generated on

the overall drug utilization patterns among different categories of Kashmiri patients that shall pave way for adoption of suitable policies and necessary interventions for improving prescribing practices as well as the quality of drug use among local population.

P041

Use of Cholera Vaccine in Pregnant Women During Mass Vaccination Campaigns

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Introduction: Cholera continues to be a major global health problem in cholera-endemic countries. Disease outbreaks usually occur wherever crowded conditions exist and water and sanitation facilities are sub optimal. Natural or manmade disasters exaggerate these conditions. Cholera is still an important cause of severe dehydration in children and adults and can be fatal within hours. The WHO Technical Note 1 issued on 13 January 2016 'Evidence of the risks and benefits of vaccinating pregnant women with WHO pre-qualified cholera vaccines during mass campaigns' highlights that cholera is more severe in pregnant women as severe dehydration in pregnant women with cholera significantly increases the risk of stillbirths or miscarriages. The currently available WHO pre-qualified cholera vaccines are killed oral cholera vaccines, Shanchol®, Dukoral® and Euvichol®. Oral cholera vaccines are generally not recommended for vaccination during pregnancy due to lack of specific prospective controlled studies conducted to investigate the safety of cholera vaccines in pregnant women and for the fetus.
Aim: To assess available evidence on the risks and benefits of OCV use in pregnant women during cholera outbreaks.
Method: Review of published studies and WHO recommendations on OCV use in pregnancy.
Results: In two retrospective cohort studies conducted among 1312 pregnant women in Guinea and among 196 pregnant women in Zanzibar who received at least one dose of Shanchol® or Dukoral®, respectively during mass vaccination campaigns, there was no association between fetal exposure to the cholera vaccine and the risk of pregnancy loss or malformation. Moreover, there is to date no evidence that killed vaccines in general are harmful to pregnant women, their fetuses or newborns. The WHO Technical Note points out that the oral cholera vaccines are not recommended but not contraindicated in pregnant women. Finally, the WHO recommends that for pregnant women in populations at high risk of cholera, the benefit of vaccination with cholera vaccine overweighs the risks.
Conclusions: In conclusion, we support the WHO vaccination strategy in cholera-endemic countries. Further the administration of Shanchol® to pregnant women may be considered by Health Care Providers after careful evaluation of the benefits and risks in the context of mass vaccination campaigns to prevent or control outbreaks. National recommendations should be considered for guidance on the use of oral cholera vaccine during pregnancy.

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P042

Knowledge, Attitude and Practice Towards Pharmacovigilance and Adverse Drug Reaction Reporting Among Postgraduate Medical Students

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Introduction: Adverse drug reaction (ADR) is major global health problem affecting both children and adults. ADRs are among the leading cause of mortality and morbidity leading to prolonged hospitalization. Hence, drug safety monitoring is the responsibility of all stakeholders of the healthcare system. Spontaneous reporting of ADRs by healthcare professionals forms the backbone of Pharmacovigilance. Therefore, there is an urgent need for sensitization about drug safety monitoring among healthcare professionals.
Aim: To evaluate the knowledge, attitude and practice towards Pharmacovigilance and ADR reporting among postgraduate medical students.
Method: A cross sectional questionnaire based study was conducted among 150 postgraduate medical students between April 2016 and May 2016 using a pre-validated questionnaire. Descriptive statistics was used for analysis.
Results: A total of 150 questionnaires were analysed. Among 150 postgraduates, 60 % were females and 40 % were males. The postgraduates who knew the meaning of Pharmacovigilance and adverse drug reaction were 64 and 90 %, respectively. Among the postgraduates 58 % were unaware of the responsibilities of pharmacists and nurses regarding ADR reporting. The most encouraging finding was 95 % of postgraduates think that reporting an ADR was necessary and 97 % of postgraduates agreed that ADR reporting will increase the patient safety. The postgraduates who encountered ADRs during clinical practice were found to be 79 %. However, 81 % of postgraduates failed to report any ADR. Busy schedule, fear of being legally responsible was the common reasons for under reporting of ADR.
Conclusions: This study suggests that even though majority of postgraduates have better knowledge and attitude towards Pharmacovigilance and ADR, the practice of reporting ADRs is inadequate. Therefore, there is an urgent need for educational intervention in the form of training programmes and CME periodically to encourage ADR reporting among the postgraduates.

P043

Cardiovascular and Gastrointestinal Safety of Paracetamol in French Population

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Introduction: Paracetamol is one of the most commonly used drugs worldwide, but very little is known of its cardiovascular (CV) and gastrointestinal (GI) safety.
Aim: To evaluate the risk of acute coronary syndromes (ACS), stroke and GI bleeding events during the use of paracetamol.
Method: Self-controlled cohort study in EGB, the 1/97 representative sample from the French national healthcare claims database, that includes 84 % of all paracetamol sales. All exclusive episodes of paracetamol use between 2009 and 2012 in patients aged ≥15 were identified. Main outcomes were ACS, stroke and GI bleeding, during the 3 months after dispensing (risk periods), or during the 3 previous months (control periods). Risks of outcome occurrence were estimated by comparing hazard rates in risk and control periods by COX proportional hazard models.
Results: There were 1,025,877 paracetamol exclusive episodes in 342,494 users (mean age 47.2 year-old; 55.8 % female). During control and risk periods, there were 684 and 825 ACS [3.2 and 3.2 per 10,000 episode-months, hazard ratio (HR) 0.91, 95 % CI (0.82–1.01)]; 340 and 374 strokes [event rate 1.6 and 1.5, HR 0.85, (0.73–0.98)]; 132 and 220 GI bleeds [event rate 0.6 and 0.9, HR 1.34 (1.08–1.66)]. In episodes without concomitant low-dose aspirin, ACS HR was 1.32, [1.16–1.49]. Stroke risk increased in patients with low CV risk, [HR 1.40, (1.10–1.79)]. Patients aged ≥60 was associated with increases in ACS and GI bleeding [1.38, (1.19–1.61) and 1.45 (1.08–1.95)].
Conclusions: Use of paracetamol in patients above the age of 60, or without cardiovascular risk or without low-dose aspirin was associated with increased risk of outcomes. Maybe the widespread use of paracetamol in the elderly should be reconsidered.

P044

Methylphenidate and Cardiac Arrhythmias: A Pharmacoepidemiological Approach in VigiBase®

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Introduction: Methylphenidate is a central stimulant amphetamine drug used in Attention Deficit Hyperactivity Disorder (ADHD) or narcolepsy.
Aim: We received a spontaneous ADR notification in a 45 year-old patient who suffered from palpitations 2 months after methylphenidate introduction for ADHD. Rhythmic holter found 3429 ventricular extra systoles (VE) with a normal cardiac examination. Three months after methylphenidate withdrawal, the number of VE was 395 and palpitations' sensations disappeared. After 10 months, cardiological evaluation was strictly normal without any VE.
Method: This "serious" case report led us to investigate in VigiBase®, the WHO Pharmacovigilance database (including more than 11 million ADRs), a putative association between cardiac arrhythmias and methylphenidate. The case non-case approach (disproportionality analysis) comparing methylphenidate to all other drugs was used. Results are shown as Reporting odds ratio (ROR) and 95 % confidence interval.
Results: After reviewing the cases, 109 cardiac ADRs (0.5 % of methylphenidate ADRs) were selected, i.e. 92 arrhythmias, 21 VE and 1 atrial fibrillation (more than 1 ADR per patient). Out of them, 87 % were "serious" (with 16 deaths). They mainly occurred in men (85 %). Mean age was 18.7 years [7–75]. Methylphenidate was prescribed in 44 % for ADHD (unknown indication in 48 %). A significant association was found between methylphenidate and ventricular arrhythmias [ROR = 1.4 (1.3–1.7)] or tachycardia [ROR = 2.0 (1.9–2.2)]. The association for ventricular arrhythmias was significantly more marked in children [ROR = 4.8 (3.9–5.8)] than in adults [ROR = 1.8 (1.4–2.4)].
Conclusions: The present pharmacoepidemiological study described significant associations between occurrence of cardiac arrhythmias (and increase in heart rate) and methylphenidate exposure. These ADRs can be explained by the pharmacodynamics profile of methylphenidate, which acts, as an amphetaminic drug, through the increase of catecholamine release. It is interesting to underline that this Pharmacovigilance signal for ventricular arrhythmias, a "serious" ADR potentially life-threatening, is more marked in children than in adults, thus justifying both a rational prescription of methylphenidate in children, but also in adults, and a regular cardiological surveillance during treatment.

P045

Use of a PharmacoVigilance Database to Investigate the Mechanism of Adverse Drug Reactions (ADRs)

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Introduction: Pharmacovigilance databases are usually used to detect new potential signals relevant for drug safety. They are seldom used for explanatory purposes, e.g. to understand the mechanisms of adverse drug reactions (ADRs).
Aim: The aim of the present study was to combine Pharmacovigilance and pharmacodynamics data to investigate the association between D2, 5HT2A, and M1 receptor occupancy and the risks of antipsychotic (AP)-induced movement disorders in order to explain the pharmacodynamics mechanism of this ADR.
Method: First, we performed a case/non-case analysis using spontaneous reports from the World Health Organization (WHO) Global Individual Case Safety Report (ICSR) database, VigiBase®. We thus measured the risk of movement disorder reporting compared to all other ADRs (expressed as a reporting odds ratio, ROR) for first (FGAP) versus second (SGAP) generation antipsychotics (APs) and the most frequently used APs. Second, we performed a linear regression analysis to explore the association between the estimated risk of reporting for individual drugs and their receptor occupancy properties for D2, 5HT2A, and M1 receptors.
Results: FGAPs were found to be significantly more associated with reporting of movement disorders in general but also with dystonia, Parkinsonism, akathisia and tardive dyskinesia than SGAPs, irrespective of gender. A significant inverse correlation was found between the ROR of

movement disorders and the receptor occupancy of 5HT2A ($p < 0.001$; $R^2 = 0.51$), M1 ($p < 0.001$; $R^2 = 0.56$) but not D2 dopamine ($p = 0.53$; $R^2 = 0.02$) receptors.

Conclusions: Using the example of AP-induced movement disorders, the present study underlines the value of the PE-PD method to explore ADR mechanisms in humans and real-life settings. In the present case, we found an inverse proportional correlation between serotoninergic 5HT2A or muscarinic M1 receptor occupancies and the frequency of reports of movement disorders induced by Aps.

P046

Underreporting Cardiotoxic Effects of Antimalarial: Reality or Illusion

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Introduction: For the treatment of malaria, a dozen of molecules are available with double or triple associations requiring monitoring their safety.

Aim: Evaluation of the notification related to the cardiotoxic effects of antimalarial drugs by comparing the report of these effects on Vigibase and the results of controlled clinical trials published on a bibliographic database as Medline.

Method: A study was performed on Medline 1965–2016 using terms mesh malaria combining toxicity or adverse effects, and adverse effects or cardiac toxicity. Only controlled clinical trials were accepted. Exclusion criteria were studies that reported adverse effects that are not related to the cardiovascular system, those that have been conducted on animals or those with an antimalarial association with plants. Vigibase was searched by using the SOC term "cardiac disorders", from MedDRA, combined to the term "antimalarial substance", from WHO Drug.

Results: Six clinical trials relating cardiotoxic effects of Halofantrine and Quinine were selected. Thus, Halofantrine prolonged significantly the time corrected QT and the other R-R intervals and QT which results in cardiac arrhythmias. On about 220 patients, the minimum average increase of QTc interval was 25.8 ms and a maximum increase of 40 ms compared to baseline [1, 2, 3]. As for Quinine, three clinical trials have shown that it causes electro-physiological changes of the heart with a prolongation of QTc. Approximately 215 patients from clinical trials combined, the average increase of the QTc interval was 12 % [4, 5, 6]. Only three cases of antimalarial induced cardiac disorders are retrieved in Vigibase. The case concerns a cardiac arrest which occurred to a 57 years old female who had taken unspecified antimalarial among other nine unspecified suspect drugs. Neither the indication, nor the duration treatment, nor the route of administration was specified. The second case is related to palpitations which occurred in a 38 years old female who had taken antimalarial (Rimetar) for an unspecified malaria. The treatment duration was 3 days and the dose given was 150 mg per day. The patient was recovered. The third case was about palpitations which occurred in 48 years old female who had taken antimalarial (Loquine) for 2 days. Neither indication nor the dosage was mentioned. The patient was recovered.

Conclusions: Underreporting cardiac effects of antimalarial drugs should prompt health professionals to report obligatory these cardiotoxic effects that can be life-threatening for patients.

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P047

Cutaneous Adverse Drug Reactions: a Retrospective Analysis from Moroccan PV Database

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Introduction: Cutaneous adverse drug reactions (cADR) are common. They have different clinical aspects and can be caused by large variety of drugs. Serious cADR are associated with significant morbidity and mortality.

Aim: To describe epidemiological characteristics of cADR and to determine the causative drugs.

Method: We retrospectively analyzed all cADR reported in the Moroccan Pharmacovigilance database between January 2004 and December 2015. Causality assessment and severity assessment were performed using validated scales.

Results: During the study period, a total of 3215 cADR reports were identified from the Moroccan Pharmacovigilance database, which represents 20 % of the whole ADR reports enrolled in the same period. The patients have a sex-ratio, M/F, of 0.6 and a mean age of 35.2 ± 21.3 years. The most frequent cADR reported were rash (38.4 %), pruritus (13.3 %) and urticaria (10.5 %). The most suspected drug groups were antimycobacterials (7.6 %), immunostimulants (3.6 %) and analgesics (2.7 %). 805/3215 (25 %) patients have serious cADR. Stevens Johnson syndrome was the most frequent reaction observed (118 cases) followed by toxic epidermal necrolysis (104 cases). Acetylsalicylic acid, allopurinol and paracetamol were respectively the main drugs implicated in both reactions.

Conclusions: The high rate of cADR observed in this study is in accordance with the literature. Serious cADR need to be identified early during treatment to improve the management of the reactions and ensure patient safety

P048

Data-recapture in Hospital Coding Databases to Detect Under-Reporting of Adverse Drug Reactions

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Introduction: Under-reporting is a serious problem with spontaneous reporting systems and the reporting rate is very low with a median under-reporting rate estimated at 94 % [1]. Capture–recapture methods, originally used to estimate the completeness of a closed wildlife population, have been used to estimate the completeness of 2 lists, [2] and have been used to estimate the completeness of reporting of harms in hospital settings [3,4]. We used this method to estimate the number of ADRs potentially missed in our local teaching hospital.
Method: We compared anonymised records of ADRs submitted from this hospital to the MHRA with the records which have been coded by the clinical coding department as ADRs using ICD codes. The details of the codes searched for are in Table 1. The data for the period April to December 2015 was analysed.

Table 1 ICD codes searched for

T88.7	Unspecified adverse effect of drug or medicament
Y10–14	Poisoning by and exposure to various classes of drugs
Y40–59	Drugs, medicaments and biological substances causing adverse effects in therapeutic use

Results: There were 77 ADR reports in our database and there were 688 reports coded as ADRs identified by our Clinical Coding department using above codes. We compared the two databases for patient age, sex, date, ADR narrative with main diagnosis. There were 16 possible or probable reports which were common to both databases. Using the Chapman estimator [5] which is less biased with small sample sizes, the estimate of the number of ADRs in the 9 month period is 3160 [95 % CI 1884, 4436] leading to an under-reporting rate of 97.6 % [95 % CI 95.9, 98.3 %].
Conclusions: The capture–recapture method is based on the assumption that the two samples are independent. This may not be the case as adverse reactions may be as likely to be captured by a spontaneous reporting system as in a hospital coding system. However, we looked at all ADRs and it is possible that minor ADRs may not have been captured by the clinical coders. We checked a random 10 % of our coding sample and 87 % of these did contain at ADR documented in the notes. This method would allow hospitals to assess the numbers of ADRs occurring without the labor-intensive use of note review which remains the gold standard.

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P049

Prescribing and Diagnostic Issues Associated with Sumatriptan Identified Through Open-ended Screening for Safety Signals in Electronic Health Care Records

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Background: Open-ended screening of temporally associated drugs and medical events in electronic health care records utilizing The Health Improvement Network (THIN) [1] detected events considered worthy of further evaluation including myocardial infarction (MI) and subarachnoid haemorrhage (SAH) associated with sumatriptan use. Preliminary assessment suggested prescribing and diagnostic difficulties may have led to these associations.
Aim: To examine the individual patient records for the two drug/event pairs for an explanation of the temporal associations.
Method: Anonymised individual patient records in THIN in which MI or SAH had been associated with sumatriptan prescriptions were examined. Each patient's past history, demographics, risk factors and recent medical events and prescriptions leading up to the date of sumatriptan prescription and up to the onset of the events of interest were assessed. The findings were compared with prescribing advice in sumatriptan labels.
Results: There were 22 THIN records for MI recorded within 2–6 months of sumatriptan prescription. Fifteen patients were male. THIN dataset commenced collection prior to sumatriptan marketing in 1993. Contraindications in the labels since 1994 [2, 3] include previous MI, ischaemic heart disease, Prinzmetal's angina and uncontrolled hypertension. In the THIN records seven patients had contraindications for sumatriptan and three others were also considered at high risk of MI.
Eleven records for subarachnoid haemorrhage (SAH) were recorded within 1 month of sumatriptan prescription. Ten of the patients were female. Presenting headaches on the day of prescription were diagnosed as migraine in five patients. Eight of the eleven had no previous diagnosis of migraine. Three of these had multiple consultations for headache within a month prior to SAH. Other warnings of possible SAH in individual patients prior to sumatriptan prescription were syncope and collapse; dizziness; head injury; blood pressure elevation [2]; prescription of diamorphine with first sumatriptan script [4].

Discussion: For MI, the striking feature of the THIN records was the prescribing of sumatriptan to known risk groups. The SAH reports indicate delayed diagnosis. The current label warns that sumatriptan should only be used where there is a clear diagnosis of migraine, taking care to exclude potentially serious neurological conditions [2].
Conclusion: Electronic health care records have proved valuable in evaluating prescribing behaviour on an ad hoc basis [5, 6]. This evaluation for sumatriptan records suggests that it may be valuable to investigate if open-ended screening can be used to systematically pinpoint prescribing issues with safety consequences in individual patient records.
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P050

Time Series Disturbance Detection for Hypothesis-Free Signal Detection in Longitudinal Observational

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Introduction: Signal detection in longitudinal observational databases (LODs) is an emerging focus of research. LODs provide a rich and complex data source for signal detection (SD). A visualization tool, called a chronograph, shows changes in a disproportionality measure, the IC, with confidence intervals, over time for specific events stratified into monthly pre/post exposure windows. Currently the interestingness of chronographs is based on discrete disproportionality calculations and subjective visual inspection/heuristics. The subjectivity of the latter motivates a search for chronograph patterns that have sufficient positive predictive value and are amenable to annotation and automated implementation. We propose an automated triage that reduces various chronograph patterns of interest into qualitative summaries, allowing clinicians to focus better on potential signals.
Aim: To implement iterative outlier detection/adjustment procedure for disturbance detection on chronographs and assess its potential in chronograph analysis.
Method: The approach classifies outlier impact into four disturbance types using the definitions of Chen and Liu: innovational outlier (IO), additive outlier (AO), level shift (LS), or temporary change (TC) [1]. We apply these to chronographs of nifedipine and localized swelling and flushing in (Norén et al. [2]) to produce change profiles.
Results: For flushing we saw an AO at onset of medication use followed by LSs back toward pre-exposure but not quite to the pre-exposure level. For swelling we saw an initial TC followed by sustained LSs with the former a bit higher than the latter, and both notably greater than pre-exposure.
Conclusions: A novel approach for outlier detection on chronographs on LOD successfully detected different outlier types for two chronographs of well-established ADRs that were clearly different from visual review. While wider testing is needed to fully understand performance, including the associated false positive and negative burdens, the results show the potential of the approach to increase efficiencies in SD in LOD. While we tested our approach on chronographs, it may apply to other visualization tools involving time trends and temporal anomaly detection. Future considerations are whether this approach captures potential signals escaping visual inspection and does outlier detection promote consistency of detection in a routine review process.
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P051

Evaluation of Antibiotic Usage at a Tertiary Care Teaching Hospital of North India

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Introduction: Hospital pharmacies usually stock a large range of medications. It is the most extensively used therapeutic facility and thus a large amount of hospital budget is spent on purchases of medicines. For rational distribution and usage of these medicines, there is a viable need for proper execution that results in efficient clinical and administrative services.
Aim: To evaluate rationality in the procedure of procurement and distribution of antibiotics from a hospital pharmacy by using WHO parameters.
Method: ABC (Selective Inventory Control), VEN (Vital, Essential, Non-essential) and DDD (Daily Defined Doses) analysis as per WHO to study the present practices for procurement, purchase and distribution of various groups of antibiotics at a tertiary care teaching hospital pharmacy. The study was conducted at Jawaharlal Nehru Medical College Hospital, AMU, Aligarh, India, after due permission of the IEC.
Results: The annual consumption and expenditure incurred on each item of antibiotic for the year 2013–2014 was analyzed and inventory control

techniques, i.e. ABC, VEN and DDD, were applied. In our study, we found only 17 injectable antibiotics in the drug formulary of the hospital pharmacy. The total annual drug expenditure (ADE) on antibiotics in the year 2013–2014 was INR 2,496,536.6. ABC analysis revealed 35.3, 23.5 and 41.2 % items as A, B and C category, respectively, accounting for 78.23, 17.90 and 3.87 % of ADE on antibiotics of the hospital drug store. However, VEN analysis showed 35.29, 58.82 and 23.53 % antibiotics as V, E and N category items, respectively as per Indian Model List of Essential Medicine 2011, which account 45.13 % (V), 44.36 % (E), and 15.53 % (N) of ADE of the hospital pharmacy. Cost per DDD of Inj. Meropenem was the highest. Its annual cost assuming 14 days course of treatment was second largest (INR 8958.89/course of treatment). Assuming 14 days average treatment course, cost per course of treatment was highest for FD combination injection of piperacillin and tazobactam at a dose of 4.5 g (INR19, 110.57).

Conclusions: Our study was compared with WHO VEN list for antibiotics as 35.29, 17.65 and 47.06 %, respectively. Thus, the scientific inventory management tools are needed to be applied in routine for efficient management of the pharmacy stores as it contributes to not only in improvement in patient care and safety but also judicious use of resources as well, particularly to identify the antibiotics needing stringent management control and to reduce antibiotic resistance.

P052

Economic Costs of Adverse Reactions to Drugs (ADRs) in Low and Middle-income Countries (LMICs)

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Introduction: The World Health Organisation (WHO) Programme for International Drug Monitoring promotes international standards in Pharmacovigilance (PV). In low and middle-income countries (LMICs), inadequate funding, regulatory oversight and healthcare infrastructure restrict national PV systems. Such restrictions can be addressed by raising awareness on the economic costs of ADRs within national governments. However, these data are available mainly for high-income countries.

Aim: The current study sought to (1) identify available data on the economic costs of ADRs in LMICs, (2) descriptively analyse available cost data, (3) illustrate strengths and limitations of existing approaches to obtain ADR related cost data in LMIC settings.

Method: Direct and indirect cost estimates related to ADRs in LMIC settings were identified from published literature. LMICs were selected according to World Bank Gross National Income per capita. Cost estimates were summarised on type of cost (i.e. direct or indirect) and were presented as reported in source publications. As a reference, cost estimates were inflation-adjusted to 2012 US Dollars based on the United States Consumer Price Index (US CPI), to allow for comparability across different estimation approaches and healthcare contexts. Strengths and limitations of methods for capturing costs were considered in terms of study design, PV method, costing approach and data sources.

Results: Twenty-one primary research articles, consisting of observational studies, clinical trials and economic evaluations, reported facility or regional level ADR-associated direct medical costs from seven different LMICs. Direct non-medical costs and indirect costs were included in five and two studies, respectively. Generally, ADR-associated costs were high, particularly when ADRs were severe, led to hospitalisation, treatment in specialised facilities and death. In some cases, individual level costs exceeded the cost of the underlying condition and the per capita national healthcare expenditure. Existing studies mainly reported prospectively obtained costs through observational studies, which investigated a wide range of drugs and related ADRs, using representative data sources from various LMIC settings. However, inconsistent costing practices contributed towards variation in observed cost estimates.

Conclusions: In general, we found limited data on ADR-associated costs in LMICs. However, available estimates suggest that the economic costs of ADRs are substantial and could support an argument for investing in PV. Clear guidance for improving the quality and reporting of costing practices can support further and more robust data collection in other LMICs. Adequate and high quality evidence on the economic costs of ADRs is required to strengthen the argument for risk minimization during therapeutic drug use in LMICs.

P053

Detection of Signals Relating to Serious Cutaneous Adverse Effects in ICSRs Moroccan Database

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Introduction: Skin disorders are among the most reported side effects with drugs. They are potentially serious in a quarter to a third of cases. In Morocco, the year 2015 was marked by the detection of two signals in relation with severe skin disorders. This is the unusually high frequency of drug hypersensitivity syndrome (DHS) induced by Allopurinol and Stevens–Johnson syndrome with Lamotrigine.

Aim: To identify the drugs the most reported in the serious cutaneous adverse effects and/or DHS, we analyzed the ICRS Moroccan database in order to identify the factors contributing and propose the risk minimization measures.

Method: Analysis of ICSR Moroccan database during a period from 1992 to April 2016 using VigiLyze software. We focalized our analysis on serious cutaneous reactions especially toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP) and also DHS. We use the data mining functionality of VigiLyze to calculate the Component Information.

Results: Among 19,173 ICSRs reported in our database during the studied period, cutaneous side effects are the most reported reactions (20.4 %). They are potentially serious in 21.6 % of cases, with a fatality rate of 1.9 %. The pair drug/serious toxiderma with a positive IC0005 are: allopurinol, paracetamol, acétylsalicylic acid, phenobarbital, lamotrigine, carbamazepine, sulfamethoxazol/trimethoprim and sulfasalazine.

Conclusions: Moroccan Pharmacovigilance system, even with a small database, is able to detect early warning signals. The evaluation of detected signals with serious drug reactions by the Technical Committee of Pharmacovigilance allowed proposing actions for minimizing these risks.

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P054

Pharmacovigilance Concerns in Kaiyadeva Nighantu—A Recognized Ayurvedic Lexicon of 14th Century

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Introduction: Pharmacovigilance is defined as science and activities related to the detection, assessment, understanding, and prevention of adverse effects of drugs or any other possible drug related problems. However the term "Pharmacovigilance" does not mentioned directly in any Ayurvedic classics but it has been emphasized repeatedly and its concept is vibrant in all classical texts like Samhita and Nighantu texts. Along with the improvement of patient care and safety, prevention of diseases is a major goal of Ayurveda. Therefore Ayurvedic literature gives details of drug–drug and drug–diet incompatibilities which should be taken care.
Aim: To review the Pharmacovigilance Concerns in Kaiyadeva Nighantu.
Method: Present review was conducted to compile access and analyze the cautions, contraindications and possible adverse effects caused by inappropriate administration of herbal drugs described in Kaiyadeva Nighantu. The reported information was analysed for the possible correlation on concept of Pharmacovigilance of current science.
Results: Kaiyadeva nighantu written during 14th century is composed of 9 vargas and contains about 896 drugs of herbal mineral and animal origin. This is also known as "Pathyapathya vibhodika", and the classification of drugs in this nighantu is not only related to medicinal plants but also various dietary items that are used regularly during that period. About 339 drugs have been found to be reported about their possible side effects when consumed wrongly or against regular protocol. The description of different food items suggests that the author was well aware about pathya kalpana and also the role of diet in etiology of lifestyle disorders.
Conclusions: The present review reports possible adverse effects due to improper administration of certain drugs and dietetic items. These mentioned possible risks of adverse effect can be minimized by adopting various guidelines and instructions mentioned in classical text.

P055

A Critical Review on the Drug Safety Issues in Sushruta Samhita—An Ayurvedic Treatise of 600 BC

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Introduction: Herbal formulations being widely accepted therapeutic agents as antidiabetics, antiarthritics, hepatoprotectives, cough remedies, memory enhancers, and adaptogens. The commonest myth regarding herbal medicines is that these medicines are completely safe, and can therefore be safely consumed by the patient on his/her own, without a physician's prescription. This belief has led to large-scale self-medication by people all over the world, often leading to disappointing end-results, side-effects, or unwanted after-effects. There is an increasing awareness at several levels of the need to develop Pharmacovigilance practices for herbal medicines. In India, Ayurveda system of medicine is well established system of traditional medicine as is based upon its own fundamental principles. Classical texts like Charak, Sushruta Samhita, etc. describes Pharmacovigilance concerns of herbal drugs.
Aim: The present paper is an attempt to emphasize the pharmaco-vigilant aspects of certain drugs of herbal origin documented in Sushruta Samhita, a text of 600 BC.
Method: All the six sthanas (divisions) of Sushruta samhita have been reviewed thoroughly and information pertaining to Pharmacovigilance aspects of drugs, diets and procedures have been noted, analysed & presented in a structured format.
Results: It was observed that shusruta samhita is comprising of six sthanas (divisions), 184 adhyayas (chapters) and deals with 700 medicinal plants, 64 preparation from mineral sources and 57 preparation based on animal sources. The samhita stresses not only on different medicines but also various foodstuffs that are consumed daily. The description of cereals, pulses, oils, cooked and prepared food items suggest that the author was well aware about pathya kalpana and also the role of diet in etiology of lifestyle disorders. Drugs has been described for their dosa provoking and teratogenicity, due in appropriate consumptions of contradictory factors.
Conclusions: The present review echoes the presence of concept of Pharmacovigilance in sushruta samhita. The present information may be helpful to help the parishioners of Ayurveda aware regarding the cautions, contraindications of certain drugs & possible side effects or complications due to inappropriate intake of diet and drugs and their preventions, etc.
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P056

A Critical Review on Pharmacovigilance Aspects of Charak Samhita: An Ayurvedic Treatises of 300 BC

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Introduction: Ayurveda, the ancient medical system, is known for its safety and effectiveness approach. Responsible for making this system safe & effective are its fundamental principles quoted in various texts e.g., samhitas (treaties), chikitsa granthas (compendia), and nighantus (lexicons). Charaka Samhita depicts instances in the context of management of various clinical conditions. But till now, there is no single hand information about the Pharmacovigilance aspects of drugs, diets and procedures reported in context of Charaka Samhita.
Aim: To collect notable descriptions on Pharmacovigilance aspects in Charaka Samhita.
Method: All the eight sthanas (divisions) of Charaka Samhita have been reviewed thoroughly and information pertaining to Pharmacovigilance aspects of drugs, diets and procedures have been noted, analysed and presented in a structured format.
Results: In the eight sthanas (divisions) of Charaka Samhita, some direct or indirect information pertaining to Pharmacovigilance aspects of drugs, diet, and procedures are available. One sthana describe the probable adverse effects of the Panchakarma procedures and their management. To this context, it is quoted that even a useful diet/drug may turn out to be harmful if not administered properly. Similarly, Charaka richly portrays a few host-related variables to be considered when selecting medications keeping in mind the end goal to

minimize unfavorable responses like the constitution of the prakriti (patient), vayam (age), vikruti (infection), satmya (resilience), satwa (mental state), ahara-shakti (digestive limit), vyayama-shakti (exercise capacity), sara (nature of tissues), sahanan (physical extents of the body) and vala (strength). Further, Charaka opines that that a solid toxin can turn into a superb solution if directed legitimately, and even the most valuable medication can act like a toxic substance if taken carelessly. Information about pathya (wholesome) and apathya (unwholesome) substances during administration of certain yogas, precautions as regards to dosage of certain medicaments, excessive use of selective drugs, contraindications of certain herbomineral drugs at specific conditions, drug and diet interaction, complications of various clinical procedures, and their management measures; complications arising from certain diseases if they are managed inappropriately, and diseases due to excessive use of six rasas delineate the aspects of Pharmacovigilance subjects.

Conclusions: The present review reflects the existence of strong concept of Pharmacovigilance during the tenure of charaka. The gathered information will be helpful to remain aware regarding the cautions, contraindications of certain drugs and possible side effects or complications due to inappropriate intake of diet and drugs and their preventions.

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P057

Process of Minimizing the Harmful Effects of Unani Drugs in the Light of Pharmacovigilance: A Unique Technology

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Introduction: Everything consumed by a man could be harmful if taken in an inappropriate manner or unprocessed, either it is a food or medicine. Pharmacovigilance is inherently practiced and followed in Unani System of Medicine (USM) which has still a very rich and effective method of drug preparation to combat side effects or harmful effect of drugs on human organs. The system is popular as a 'safe medicine', having no or minimum side effects to human body.

Hypothesis: If the method of drug preparation is not followed in the light of traditional medical ethics and as per the Pharmacopeial guidelines, then it would expect to have harmful effect.

Methodology: The present paper reviewed the Pharmacovigilance practices in the Unani system of Medicine.

Observations: Every safe practice is followed since its origin to minimize the adverse effects of drugs in USM before it is consumed. The motto of USM is to treat disease as well as patient as a whole, which has been very profound basis of its popularity in the Indian subcontinent [1]. Medicines in USM are screened prior to administration on the basis of patient's degree of 'humoral temperament'. Drugs which may be toxic undergo various processes so that the harmful effects can be minimized to a lesser degree. Along with this, various other parameters such as age of the patient, season, gender, temperament of drugs into 1st, 2nd, 3rd and 4th degrees, are checked before prescribing any drug [2]. These factors help in reducing the adverse effects to a higher extent. The present paper deals and elaborates in details all the methods of drugs preparation including in vivo and vitro techniques being used in Unani system of medicine for vanishing their unwanted actions.

Conclusion: Unani drugs of 3rd and 4th degree category are very harmful having toxicity and sometimes irreversible toxicity and if they are processed for their detoxification correctly with proper identification may be minimized these known unwanted or toxic effects.

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P058

Unani Medicine: Impediments and Solutions

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Introduction: Traditional systems of medicine are an integral part of the cultural fabric of India. Ayurveda, Unani and Siddha are household names and do not need any introduction. However, their prevalence and popularity are grossly underestimated in the second most populous country in the world.

Method: The true estimates of the people relying on a combination of Ayurveda, Unani and Siddha may not be known. Their presence is still regarded as a 2nd class citizen; the reasons being they are less hip, less glamorous and do not command the strong appeal due to their inability to treat acute medical conditions, and the lack of surgical practices.

Observation: Despite being very effective in the treatment of chronic and functional diseases, the systems failed to market themselves effectively. Also, the stubbornness of the practitioners of these systems not to evolve with the changing times has added to their woes. Unani system of medicine is the precursor of the modern allopathic medicine, but is stagnated in the twelfth century practices. The government of India has been spending millions of rupees every year for the past 40 years, but the results are less than encouraging.

Conclusion: The presentation would discuss some of the impediments to the progress of Unani medicine and offer some solutions.

P059

How far Ethanolic Extract of Myristica Fragrans is Safe in Morphine Dependence—An Experimental Study

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Introduction: Morphine addiction is worst affected socio-economic problem. It causes physical dependence resulting into difficult withdrawal during

de-addiction. Numbers of therapeutic medicines have been described in folk medicine to overcome the addiction. Myristica fragrans is one of the important spices used as medicine. Its usefulness is reported in many medical conditions [1]. Psychoactivity as hallucinations, euphoria, unreality and delusions is documented since middle ages [2]. It is abused as a cheap substitute for morphine narcotic drugs particularly in adolescents [3] since 12th century [4]. The present study is done to evaluate the role of ethanolic extract of Myristica fragrans (EEMF) in morphine dependence.

Aim: To evaluate efficacy and safety of EEMF in morphine dependence.

Method: Wistar albino rats were made moderate and severe morphine dependence by administering morphine sulphate in dose of 10 mg/kg (ip), bd for 4 days and by increasing doses of 10–100 mg/kg (ip), bd for 7 days respectively. Signs of spontaneous abstinence syndrome were recorded 12 h in both studies after last dose of morphine for 30 min and quantified by 'counted' and 'checked' signs. EEMF was administered po in different regimen: (a) EEMF 200 mg/kg along with morphine twice daily for 4 and 7 days in moderately and severely induced morphine dependence group respectively. (b) EEMF 400 mg/kg (po), single dose 10 h after the last dose of morphine in both moderately and severely induced morphine dependence rats.

Results: Oral administration of EEMF in both study groups caused significant reduction in the scores of counted and checked signs of morphine abstinence syndrome as compared to active morphine control group. The reduction was significantly more in regimen 'a' as compared to regimen 'b'. Acute toxicity study showed the drug was safe and no abnormal behavioral changes were found.

Conclusions: EEMF significantly reduced mean scores of various 'counted signs' and 'checked signs' of morphine withdrawal syndrome and might give a solution as a substitute therapy in morphine de-addiction. If marketed, rigorous PMS is needed to prove its fool proof safety.

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P060

Post-marketing Safety of Two Different Formulations of Deferasirox, Film-Coated Tablet (FCT) and Dispersible Tablet (DT), A Comparative Assessment

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Introduction: Deferasirox is a once-daily oral iron chelator approved for transfusional iron overload and non-transfusion dependent thalassemia syndromes. Medicines for womenNovartis launched the original formulation in November 2005 as DT. To further improve palatability and compliance, especially for young children, Novartis developed a new formulation, FCT, launched in the US on 01 Apr 2015. Clinical trial exposure to FCT is currently limited compared with experience with DT.

Aim: To complement clinical trial data and support the safety profile of FCT for ongoing submissions, post-marketing data from the US were used to assess the safety of FCT vs. DT.

Method: A retrospective safety assessment of the Novartis safety database (NSD) was performed using reporting rate [events reported by preferred term (PT)/patient exposure]. Results are reported using the reporting rate ratio (RRR), with risk ratio analysis as a measure of relative effect with 95 % confidence intervals (95 % CI) and p-values (two-sided exact test). The search strategy in NSD involved two searches. Search 1: all adverse events (AEs) reported in the US for FCT and DT from 01 Apr 2015 to 31 Jan 2016 (10M-after). Search 2: all AEs reported in the US for DT from 01 June 2014 to 31 Mar 2015 (10M-prior).

Results: Searches retrieved (cases/events) 95/189 for FCT, 375/964 for DT 10M-after; and 636/1511 for DT 10M-prior. No associations were demonstrated against FCT. Overall results [RRR (95 %CI)] show 33 associations against DT in 886 PTs analysed in two pools analysed; 96.3 % of PTs did not show significant difference. Pool 1 (FCT-10M-after vs. DT-10M-after) with 18 associations against DT for: total cases 0.28 (0.23–0.35); abdominal discomfort 0.41 (0.17–0.97); abdominal pain 0.07 (0.01–0.56); anaemia 0.09 (0.01–0.71); asthenia 0.26 (0.07–0.90); death 0.22 (0.09–0.53); diarrhea 0.36 (0.21–0.64); drug intolerance 0.04 (0.00–0.72); fatigue 0.03 (0.00–0.42); gastrointestinal disorder 0.22 (0.06–0.77); haemoglobin decreased 0.10 (0.01–0.78); malaise 0.17 (0.05–0.56); nausea 0.38 (0.19–0.76); off-label use 0.06 (0.00–0.95); pneumonia 0.03 (0.00–0.51); pyrexia 0.18 (0.04–0.83); sickle cell crisis 0.05 (0.00–0.78); and vomiting 0.39 (0.15–0.99). Pool 2 (FCT-10M-after vs. DT-10M-prior) with 15 associations against DT for: total cases 0.29 (0.23–0.35); abdominal pain upper 0.12 (0.02–0.90); anaemia 0.13 (0.02–0.97); death 0.13 (0.06–0.30); diarrhea 0.43 (0.25–0.73); disease progression 0.13 (0.02–0.97); fatigue 0.04 (0.00–0.63); haemoglobin decreased 0.12 (0.02–0.90); malaise 0.13 (0.04–0.40); myelodysplastic syndrome 0.08 (0.01–0.62); pneumonia 0.04 (0.00–0.66); pyrexia 0.20 (0.05–0.87); renal failure 0.23 (0.05–0.98); serum ferritin increased 0.13 (0.02–0.97); and sickle-cell anaemia crisis 0.05 (0.00–0.76).

Conclusions: This post-marketing safety assessment provides evidence that the safety profile of both formulations was similar, with a tendency for better tolerability in FCT, particularly in the gastrointestinal tract. These results however, should be interpreted with caution as the number of cases in FCT was small. Further analyses are required involving longer use and greater patient-exposure to confirm these findings.

P061

Did the Safety Warnings Minimize the Risk of Antipsychotic-Related Stroke in Elderly People with Dementia?

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Introduction: In March 2004, EMA and the MHRA (UK) launched a safety warning on the risk of stroke with olanzapine and risperidone use in

dementia, later extending the risk to all antipsychotics (APs). It is not known if these warnings minimized the risk of stroke associated to APs in this population.
Aim: To investigate the risk of stroke among older patients receiving APs before and after the March 2004 safety warning.
Method: A case–control was nested in a cohort of incident AP users (no AP use in the year before the first AP prescription) in The Health Improvement Network (THIN) from 2000 to 2012. Cases were >65 and <89 years, had an incident stroke (the date of which was the index date-ID), had no cancer anytime. Up to 10 controls were matched to every case on age, sex and index date (which was the same for cases and matched controls). AP use was categorized as current (ID to 30 days prior), recent (31–180 days prior to ID), past (181–365 days prior to ID) and distant past (>365 prior to ID: reference group). The first and last AP in the study period was used to classify persons as treated before, after and across the March 2004 warning. A preliminary crude conditional logistic regression model was run on the whole study period and stratified by time period (AP treatment before, after and across the warning) to estimate the odds ratio (OR) along with 95 % confidence intervals (CI). Risk analyses adjusted for potential confounders are ongoing.
Results: Overall 875 cases and 5610 controls were identified. There were 2626 persons treated with APs before the warning, 2880 persons treated after the warning and 979 treated across the warning. When no temporal restriction was applied, the crude risk of stroke was 2.01 (1.73–2.49) for current AP users, 1.59 (1.21–2.08) for recent users and 1.18 (0.86–1.63) for past users. The risk of stroke among current AP users was higher before the warning [OR: 2.69 (1.79–4.03)] than after the warning [OR: 1.63 (1.21–2.18)]. The risk of stroke was not significant considering persons treated across the warning [OR: 0.75 (0.36–1.56)].
Conclusions: Accounting for the safety warning unmasked a different risk in AP users not exposed to the warning compared to those exposed. This may be due to changes in the underlying population, the use of lower drug dosages or shorter duration of treatment.

P062

Regionalization of Pharmacovigilance in Morocco

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Introduction: In Morocco, the National Pharmacovigilance system is organized and supported by the Ministry of Health. It includes the national level, the National Pharmacovigilance Centre (CNPV), the Pharmacovigilance Technical Committee and the National Commission of Pharmacovigilance. Regionally, a person (doctor or pharmacist) formed in Pharmacovigilance is designated Regional Pharmacovigilance corresponding (CRPV) by the Regional Director of Health in coordination with the National Poison Center and Pharmacovigilance.
Aim: Development and strengthening of Pharmacovigilance at the Souss Massa region.
Method: At the Souss-Massa region Pharmacovigilance was strengthened in 2015 by the assignment of a regional correspondent responsible for collecting notifications of adverse effects of drugs and other health products in the region, validate and analyze each reported adverse event, issue responses to notifiers and proceed to send regular CNPV any event, produce and maintain the basis of regional data on adverse events, participate in signal generation and validation alert and also the implementation of risk minimization measures.
Results: During 2015, we identified 110 notifications related to the use of health products in the Souss-Massa region with an increase of 67 % by comparison with 2014. Two cases of information requests have reported drug interaction between third-line antiretroviral and antibacillary under coinfection HIV and tuberculosis. The cases of adverse reactions (129) were spontaneously reported in 46.9 and 53.91 % were collected during an antiretroviral change study at the regional referral center for care of PLHIV in Agadir presented at the technical Committee meeting of Pharmacovigilance (PV-NAP). Two cases were reported materiovigilance Taroudant by the hospital and a case vaccinovigilance notified by the Agadir regional hospital. The Agadir CRR is leading, it notified (73.63 %) followed CDTMR Inzegane and Agadir (16.36 %), the regional cancer center (5.45 %) and hospitals of Agadir and Taroudant (4.54 %). Notifiers are doctors (infectious disease, oncologist and Pneumo-phthisiologists) (92.72 %) and pharmacists (7.27 %).
Conclusions: The organization of Pharmacovigilance can be centralized or decentralized. Experience has shown that decentralization of the activity through the creation of regional centers improves the exchange of information with health professionals and thereby provides a comprehensive view on the situation.

P063

Misuse, Abuse and Diversion of Instanyl® (Fentanyl Nasal Spray) in France

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Introduction: Instanyl® (fentanyl nasal spray) received European market authorisation in July 2009 for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain, with precise instructions on indications for use and dosage.
Aim: The study objectives were to evaluate patient-reported misuse, abuse, and diversion of Instanyl® in real-life in France.
Method: Cross-sectional observational study of patients with an Instanyl® dispensation from a non-hospital pharmacy. An anonymous self-administered questionnaire was distributed to patients at the time of drug dispensation between 27 July 2011 and 12 November 2012. The questionnaire collected data on indication, contraindications, Instanyl® use, and previous completion of the questionnaire.
Results: Among the 272 eligible questionnaires (at least one item completed in addition to age, gender, time since first prescription, and absence of previous completion of the questionnaire), all patients were adult and 95 % declared misuse. Among the 160 patients who declared having cancer, 94 % declared misuse: 76 % declared at least one indication/contraindication misuse and 86 % at least one posology misuse. Widening the definition of use for breakthrough pain to use for both breakthrough and chronic pain in cancer patients, reduced the indica-

tion/contraindication misuse (63 %), but when posology misuse was also considered this did not markedly change overall misuse (93 %).
Abuse of Instanyl® (using the drug for emotional reasons, relaxation, or sleep disorders) concerned 21 patients (15 with cancer, and 6 without); diversion (passing the drug to another person) concerned 2 patients (1 with cancer and 1 without).
Conclusions: Misuse of Instanyl® was widespread. Nearly half reported not to have cancer, and among those who did, only a few used this drug correctly. There seems to be a communication deficit as to the proper prescribing of this drug, and its proper use when prescribed.

P064

The Effectiveness of Risk Minimization Programs (RMinPs) for Lenalidomide & Pomalidomide in Turkey

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Introduction: Lenalidomide (Revlimid®) and pomalidomide (Imnovid®) are immunomodulatory drugs and structurally related to thalidomide which is a known human teratogen that causes severe life-threatening birth defects. To prevent fetal exposure to lenalidomide and pomalidomide they are only available in Turkey under the conditions of a comprehensive risk minimization programme [Pregnancy Prevention Program (PPP)]. A key component of the PPP is the Prescription Authorization Form (PAF), which documents the patient's childbearing potential status, the date/result of pregnancy test (where applicable) and the physician's confirmation of patient counselling.
Aim: To monitor the effectiveness of RMinPs for lenalidomide and pomalidomide since the approval of the products in Turkey.
Method: The PAFs for lenalidomide and pomalidomide received by Celgene Turkey during Aug 2010–May 2016 were collected and relevant key data was analysed.
Results: During the study period, a total of 44,702 PAFs from 6382 patients and 156 patients registered in the lenalidomide and pomalidomide PPP respectively were received and assessed. Of the total patients, 3624 were males and 2914 were females. There were 101 women of childbearing potential (WCBP), constituting 1.55 % of the patient population. A total of 6256 (96 %) patients were prescribed lenalidomide or pomalidomide within the approved indications. All PAFs (44,702) underwent a verification check to confirm that the following actions had been performed: documentation of patient's childbearing potential and confirmation that the physician had counseled the patient. For women of childbearing potential, the date of the pregnancy test and the results were provided. All pregnancy results had been confirmed as negative for WCBP patients before any product was dispensed. No pregnancy reports in female patients or in the female partners of male patients under lenalidomide or pomalidomide treatments originated from Turkey were received.
Conclusions: Lenalidomide and pomalidomide are expected human teratogens. A well-executed PPP is vitally important for preventing fetal exposure to lenalidomide and pomalidomide. Regular monitoring of compliance with the PPP requirements is critical to ensure that the program is meeting its objectives and to identify enhancement opportunities as needed. In Turkey, a high compliance to the PPP (100 % compliance) is demonstrated following the PAF verification process. To support PPP compliance, Celgene Turkey has refined the PPP process including establishing enhanced local Additional Educational Materials, and introduced further initiatives to facilitate PPP awareness at the pharmacy level.

P065

The Role of KIDS in Pharmacovigilance Field

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Introduction: In Korea the spontaneous adverse drug event reporting system has been operated since 1988 for the domestic events and in 2012 KIDS was established for the efficient and organized of the drug safety and relevant information to implement all the affairs concerning the drug safety management with Ministry of Food and Drug Safety (MFDS).
Aim: To aim at promoting international cooperation by introducing the role and tasks of Korea Institute of Drug Safety and Risk Management (KIDS) in Pharmacovigilance (PV) field.
Method: We would like to introduce the role and tasks of KIDS in PV field.
Results: At the beginning of establishment in 2012, KIDS set up Korea Adverse Event Reporting System performing the tasks on 'collecting, managing, analyzing, evaluating, providing' of the domestic adverse drug events. From 2013 to 2015, approximately 200,000 reports were collected each year and the Individual Case Safety Reports (ICSRs) are sent to WHO-UMC periodically. As of May 2016, Korea reports the third-highest number of ICSRs to VigiLyze following US and UK. The main reason for the number of reports lies in KIDS' nationwide operation of 27 regional PV centers composed of university hospitals in each region, which contribute to the qualified reports with higher completeness. Therefore in the completeness evaluation by WHO-UMC, the reports data from Korea score higher than world average. KIDS finds grounds to support drug safety administrative action by performing signal analysis and evaluation derived from collected AE data. Since August 2014, serious adverse drug reactions occurring in foreign countries are mandatorily reported from pharmaceutical companies. Meanwhile, KIDS used domestic AE report data only for signal analysis and evaluation, but perform integrated signal analysis and evaluation using both domestic and foreign ones for supporting safety administrative action. For the integrated signal analysis of domestic and foreign AEs, KIDS and MFDS are jointly developing an algorithm consulting internal PV specialists and referencing overseas regulatory agencies. In addition, KIDS plans to integrate the domestic and foreign reporting form and harmonize with ICH-E2B (R3) format in accordance with the global circumstances.
Conclusions: After establishment, KIDS achieved remarkable growth for 4 years by organizing and enhancing the PV system. In order to be among the world's top 5 specialized institution in drug safety management, KIDS will continue developing the PV system and promote further cooperation with overseas regulatory agencies and international drug safety society.

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P066

Communication Tool for Better Safety Outcome in Using Medicines

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Introduction: Health problems related to medicinal products, particular after using them such as side effect, adverse drug reaction (ADR), adverse effect (AE), etc. Some problems cause serious illness and death which lead to other aspects for example, patients sue doctors, NGOs sue hospitals or health service organizations. It has been accepted that communication between health professionals (doctor, pharmacist, dentist, nurse) and patients is important because effective treatment come from effective messages. In Thailand, Health Product Vigilance Center (HPVC) is the national center for collecting, validating, making assessment all AE reports from hospitals and pharmacies around country. Most of reports which have been sent to HPVC come from pharmacists working in hospitals or pharmacies. We, HPVC, concern that if pharmacists have communication tools for using while they talk to patients, it will help patients for better understanding in using medicines. So we developed info graphic guideline book entitled "sick, recommendation, cautions" which was translated to ASEAN countries languages plus Chinese, English, and Russian. Hopefully, the guideline book using by pharmacists will affect behavioral changes in patients and better understanding medicine using.
Aim: To evaluate the attitude of pharmacists to info graphic guideline book.
Method: Survey design. We invited 100 hospital-pharmacists to the meeting and set up the program for them to comment on each part of the info graphic guideline book. Then we classified all comments into three groups; (1) positive or negative, (2) contents, (3) understanding.
Results: 50 pharmacists (50 % of invited people) participated in the meeting and made useful comments on info graphic guideline book. Most of participants felt positive to the book, and thought it helped them giving better services to patients or customers. The contents were appropriate and the participants suggested to add some new items such as ka-ra-o-ke under each languages. For understanding, almost pharmacists were familiar with contents in the info graphic guideline book and they appreciated to use it with customers, particular foreigner customers from Myanmar, Russia, and China. They said the book was friendly use and their customers trusted them higher when they spoke the same language.
Conclusions: To give better services to patients and let them understand how to use medicines properly, cautions, and also side effects, AE, ADR may happen anytime of careless. When health professionals have useful communication tools such as Info graphic guideline book for explanation complex medical words to easy and friendly words to patients, it probably encourage patients to change behavior finally.

P067

Routine Infant Vaccination and Stevens Johnson Syndrome

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Introduction: Stevens–Johnson syndrome (SJS) is an immune-complex mediated hypersensitivity that manifests as an acute, severe rash involving both the skin and the mucous membranes. Drug-induced and malignancy-associated SJS is more commonly implicated in adults, while infection-induced SJS is more commonly implicated in children. Case reports exist which describe SJS after vaccination.
Aim: To investigate a potential relationship between SJS and routine childhood vaccination.
Method: Clinical review of individual case safety reports (ISCRs) within the age range of 0–23 months included in VigiBaseÂ® up to 1 May 2016 reporting the MedDRA Preferred Term "Stevens Johnson Syndrome" and the following vaccines: J07AF, J07AG, J07AJ, J07AL, J07AM, and J07BC.
Results: As of 1 November 2015, there were a total of 40 unique reports of Stevens–Johnson syndrome in association with routine childhood vaccines used in infants through the age of 23 months. A total of 14 cases support the signal; they were serious (requiring hospitalisation), reported no concomitant live attenuated or meningococcal vaccines or other medications, and described reasonable time to onset between vaccination and symptoms (same day to 9 days). Seven of the reports describe SJS after the receipt of a combination of vaccines; seven reports describe one suspect vaccination (pneumococcal vaccine $\times 4$, Hib $\times 1$, and hepatitis B vaccine $\times 1$). Countries of origin include: Australia, the United States, Venezuela, and the United Kingdom. Nine cases were reported as "non-serious", which questions the appropriateness of the AE as true Stevens–Johnson syndrome. Fifteen cases reported concomitant vaccination with meningococcal vaccine or a live attenuated vaccines for measles, mumps, rubella and varicella zoster. Nine cases reported either recent past use or concomitant administration of other medications known to be associated with Stevens–Johnson syndrome, including paracetamol, antibiotics and anticonvulsants.
Conclusion: The overall benefit/risk of vaccination at the population-level is unaffected by these very rare, spontaneous reports of SJS. However, such rare AE reports may not be random, as there is growing evidence that immunological responses to vaccines are genetically predetermined.
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P068

Agranulocytosis Around the World

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Introduction: Agranulocytosis is a serious adverse drug reaction (ADR) that is defined as a decline in absolute neutrophil count to <0•5 × 109/L (<500/μL). It is causally related to over 125 nonchemotherapy drugs, and among the most well-documented are thiourea drugs used for the treatment of hyperthyroidism; other drugs as dipyrone, antibacterials, clozapine are also frequently associated with this condition. Patients often present with symptoms of infection such as fever, chills, and myalgias. Left untreated, sepsis will develop in approximately two-thirds of patients. Despite appropriate management, the mortality rate of agranulocytosis induced by non-chemotherapy drugs is 4–5 %. Thus, it is of importance the reaction to be identified and accordingly reported.

Aim: To know how and why agranulocytosis is reported as an ADR in different areas of the world.

Methods: A search was conducted by using VigiLyze. VigiLyze is a powerful search and analysis tool that provides access to more than 13 million Individual Case Safety Report (ICSR) VigiBase®, a World Health Organization's database; these reports are submitted through National Pharmacovigilance Centres by more than 100 countries around the world.

Results: There were 103,446 cases of agranulocytosis up to May 2016 in the database; the total number of reports was 13,000,923 by that date. The overall estimate in the database was eight cases of agranulocytosis every 1000 reported cases of whatever condition. In the countries considered this estimate for agranulocytosis ranged between 1/1000 (Mexico) and 30/1000 (Japan). The overall ratio between the proportions of the reaction in females and males was 1.2; it varies from 1 in USA up to 1.6 in China. Table I presents the data for those countries surveyed.

Conclusions: Though the reporting of a particular reaction depends on many factors, the rate does vary 30 times among the countries surveyed. A different susceptibility for this condition among different population should be evaluated.

Table I Agranulocytosis in different countries Source, VigiBase

Country	Agranulocytosis/total[a]	Estimate[b]	Female/male
Sweden	2001/145,182	14/1000	1.5
Peru	97/46,648	2/1000	1.1
Spain	4052/257,347	16/1000	1.0
Mexico	55/72,322	1/1000	1.5
Brazil	51/4754	11/1000	1.6
Portugal	375/30,433	12/1000	1.6
USA	31,525/6,377,795	5/1000	1.0
China	12,597/506,167	25/1000	1.6
Japan	6744/223,000	30/1000	1.1
All countries	103,446/13,000,993	8/1000	1.2

[a] Number of cases of agranulocytosis included in the database/total number cases of whatever condition

[b] Number of cases of agranulocytosis per 1000 cases of whatever condition in the database

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Pharmacovigilance and Drug Safety: Practical Difficulty and Challenges

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Introduction: Today's increasing pace of innovation in the Life-Sciences industry is resulting in ever larger number of drugs and medical devices coming to the market every year. Ensuring the safety and efficacy of pharmaceuticals and biotechnology products is one of the top challenges in healthcare today. Pharmacovigilance is instrumental in helping to ensure patient safety for both newly released drugs and those that are well established in the market. However, while Pharmacovigilance procedures are strictly regulated in the clinical trial setting, post-marketing adverse event reporting is not well implemented or enforced. An effort has been put up here to highlight the Practical Problems and Challenges in the field of Pharmacovigilance and Drug Safety.

Aim: To identify practical problems and challenges in the field of Pharmacovigilance and drug safety.

Method: A conceptual review of the Pharmacovigilance has been taken into consideration for monitoring the effects of Ayurvedic drugs after they have been licensed for use, especially in order to detect previously unreported adverse effects. There is a gripping need for introducing new therapeutics forces regulatory authorities to approve drugs when reasonably adequate safety profile has been determined.
Result: Pharmacovigilance facing the challenges in healthcare delivery because of not getting priority. Biasness of drug in healthcare delivery system is also a big issue. Poor staffing, poor funding and mostly political pressures creating barrier in implementing of Pharmacovigilance programme. All these criteria are to be taken into consideration for revolving out practical difficulties and challenges.
Conclusions: A rigorous Pharmacovigilance program, incorporating and supported by all health professionals involved would eventually reassure the community regarding their safety. Adverse events can be brought to a minimum level by having sound knowledge about the side effect of the drugs. Improvement of communication regarding Pharmacovigilance between public and health professionals creates awareness and adverse occurring can be minimized. Proper knowledge on Pharmacovigilance would help to health professionals to understand the effectiveness or risk of medicines that they prescribe and ensure a better healthcare to patient and solving out the practical difficulties and challenges.

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P070

Safety Profile of Idarucizumab, a Reversal Agent for Dabigatran: Setting-up a Regional Observatory

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Introduction: Idarucizumab is a monoclonal antibody developed to antagonize the direct oral antithrombin inhibitor, dabigatran (Pradaxa®). It has been authorized at the end of 2015, by the EMA and the FDA for the management of uncontrolled or life-threatening bleeding or for emergency surgery in dabigatran treated patients. Preliminary results, on the first 90 patients of the clinical trial (CT) REVERSE-AD [1], have shown an immediate reversal anticoagulation with normalization of coagulation parameters. As the primary end point was purely biological, the transposition of these results in clinical routine practice is interesting. Moreover, in the CT, five cases of thrombosis, a mortality rate of 17.6 %, and a rebound in dabigatran concentrations after idarucizumab administration in 22 patients is questioning.
Aim: To collect clinical and biological information about idarucizumab use, indication, efficacy and safety.
Method: All hospitals corresponding to two Pharmacovigilance centers (CRPV) and likely to use idarucizumab were identified. We focus on hospitals having healthcare facilities with emergency, intensive care, surgery, digestive and vascular neurology units. For each hospital, we contacted pharmacists, emergency physicians, anesthetists and hematologists. After their consent, a meeting was organized to explain the inclusion and follow-up of patients, using a A specific data collection sheet.
Results: A total of 10 hospitals were contacted and all agreed for participating. From February 1st to May 1st, five patients (3 men, median age 79) were included, treated with dabigatran for atrial fibrillation. Four patients received one idarucizumab administration: two for digestive hemorrhage, one for subdural hematoma and one for emergency cardiac surgery. The other patient received the first dose of idarucizumab for ischemic colitis surgery and a second dose, 2 days later, for new surgery. After idarucizumab administration, for the four patients tested, the dabigatran concentration was below 30 ng/ml in less than 1 h. However, a rebound of dabigatran concentration was observed in all four patients. Dabigatran was not reintroduced in any patient.
Conclusions: Idarucizumab is the first specific antidote of a direct oral anticoagulant available. This study emphasizes the importance of a biological and clinical monitoring as some questions are still pending. Moreover, in some circumstances (massive overdoses or acute renal failure) a fixed dose may not be adapted and there is insufficient data on the risk of hypersensitivity, in particular for patient requiring two doses. To date, all hospitals contacted agree for participating and in the next weeks, this observatory will be extended to the overall 4 CRPV of Paris area.

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P071

A Systems-based Model for Better Defining the Pharmaceutical System (STAMP)

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Introduction: A general model of complex systems can be expressed in terms of a hierarchy of progressively complex organization levels where each level has emergent properties. In control theory, open systems are viewed as interrelated components that are kept in a state of dynamic equilibrium by feedback loops of information and control. Controllers use process models to determine control actions. Regulatory or control action is the imposition of constraints upon the activity at one level of a hierarchy, which define the "laws of behavior" at that level. Controllers use feedback to update their process/mental models of the system as the system evolves.
Aim: We present a systems-theoretic model, based on both proactive and reactive practices, integrating information from all stakeholders (i.e. regulatory bodies, industry; healthcare professionals; end-users' experience), deviation investigation reports and data from reporting systems.
Method: By applying Systems-Theoretic Accident Model and Processes (STAMP), we can define an internationally applicable model for better regulation and more effective safety system using methotrexate and risk of leukopenia as a case study.

Results: A model based on STAMP to demonstrate the components of each loop. Controller: regulatory bodies, marketing authorisation holders who define control actions and regulations through control algorithms and set points. Actuators: those who have to apply and adhere to regulations such as the license holders. Controlled process: inputs, outputs, disturbances. Sensors: those who measure the variables of each process and feed information back to the controller and share information between all stakeholders.
Conclusions: To assess the benefit/risk of medicines, regulatory bodies should consider all hierarchical levels of the systems involved, emergent properties (e.g. safety, risk awareness), dynamic interactions among operators and communication between the inner and the outer environment. By using STAMP, the purpose of imposing control actions is not to limit the behaviour of the system and its components, but to treat an accident as a control problem. STAMP identifies organisational factors and factors and the role they may play in an accident. Without this broader view of the accident (or of the organisation before suffering any damage), only the symptoms of the organisational problems may be identified and eliminated, without significantly reducing risk of a future accident caused by the same systemic factors, but involving different symptoms at the lower technical and operational levels of the hierarchical control structure.
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P072

A Project on Adverse Drug Reactions Due to Medication Errors in Hospital

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Introduction: A medication error is a failure in the treatment process that leads to, or has the potential to lead, to harm to the patient [1]. Medication errors can occur in different phases of the therapeutic process (prescribing, distribution, administration and monitoring) and have significant impact on morbidity and mortality. When harm arises from a medication error it is potentially preventable [2].
Aim: To analyze and limit through educational audit and specific tools adverse drug reactions (ADRs) due to medication errors in hospital.
Method: A prospective observational study was conducted on patients admitted to seven different wards (four internal medicine and three geriatric wards) of the University Hospital of Verona (Italy). A three-phase study was carried out. In phase 1 three specialized monitors registered all suspected ADRs occurred and reviewed all inpatient charts during a 3-month period. Concomitantly ADRs were evaluated and confirmed by using a standardized method by two different panels of experts. Type, incidence, severity, and preventability of ADRs were assessed. In phase 2 educational audits directed to health professionals were conducted, providing tools and strategies to improve a safe prescription. Phase 3 retraced the same procedure of the first phase. A statistical analysis of data collected to evaluate the impact of phase 2 in reducing ADRs from medication errors was performed. Health professionals were invited and supported in sending observed ADR reports to national Pharmacovigilance system.
Results: During phase 1 and 3 1474 patients (mean age 77 years, DS ± 14.9) and 1521 patients (76 years, DS ± 15.5) were enrolled respectively with a scarce prevalence of women. During phase 1 a total of 190 ADRs occurred in 113 hospitalized patients while 132 ADRs (occurred in 54 patients) were causes of hospital admission. Twenty-nine percent of ADRs during hospitalization were assessed as preventable. During phase 3 124 ADRs occurring in 76 patients, had caused admission to hospital, while 135 patients showed at least 1 ADR during hospitalization, 264 ADRs in total. Out of these ADRs 11 % were assessed as preventable. Between phase 1 and 3 there was a large reduction of preventable ADRs. Wrong antibiotic or antithrombotic therapy, and excessive use of diuretics were the most relevant problems reported and the drugs most involved were fluoroquinolones, sartans, furosemide, and heparins.
Conclusions: The study confirms a quite high incidence of medication errors as a cause of ADRs in hospital. The prevention of medication errors is an important task to improve the patient health and to reduce health care costs. Strategies can be adopted in order to try to minimise risks.
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P073

Francophone Pharmacovigilance Inter Country Training Course: Skills Development Tool in the Countries

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Introduction: To improve the situation of Pharmacovigilance in Francophone countries, especially those with limited resources, the Moroccan Pharmacovigilance Center was requested by the World Health Organization to organize the francophone Pharmacovigilance training course for French speaking countries since 2007.
Aim: The aim of our work is to assess all editions of the francophone Pharmacovigilance inter country training course from 2007 to 2016.
Method: This is a retrospective study of all editions. The analysis was based on the study of the evolution of the number of participants by years, their distribution according to countries and their status. This evaluation also concerned the duration of the course, the adopted pedagogical method, the distribution of interveners and financial support.
Results: From 2007 to 2016, 10 promotions were formed. The 179 trained participants belong to 26 countries, including 24 African, one European and one American. A ranking of countries according to the number of participants showed that first place goes to the DRC followed by Burkina Faso and Côte d'Ivoire. Senegal is in 3rd position. The distribution of participants according to their profiles showed that 50.28 % were doctors, 45.81 % pharmacists and 2.79 % of nurses. Other profiles accounted for only 1.22 %. The doctor/pharmacist ratio calculated for all the promotions showed a predominance of physicians in the first edition with a ratio of 19. This trend reversed gradually to 0.47 for the 10th edition. With the exception of 2008, 2009 and 2010, the

duration of the course was 2 weeks. For all editions, theoretical courses represented 65.50 %, working group 19.27 and 17.28 % participants' presentations. 55.02 % of the interveners belong to the CAPM followed by 20.57 % from the Moroccan academics and 6.22 % from the WHO and from the pharmaceutical industry. A ranking based on the number of participants supported by donors showed that WHO is in the first position followed by the pharmaceutical industry and in 3rd place there is the Global Fund.

Conclusions: The Moroccan Pharmacovigilance Center will pursue its training activities to put in place and strengthen Pharmacovigilance systems in French-Speaking countries.

P074

Identification and Resolution of Drug Related Problems (DRPs) in Respiratory Medicine Patients

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Introduction: Worldwide, role of pharmacist is evolving and the focus is briskly shifting from product to patient, from bench side to the bed side. Healthcare facilities of the region too need to keep pace with fast changing trends in pharmacy profession.

Aim: To identify, resolve and prevent drug related problems and optimize drug therapy outcomes through interventions by a clinical pharmacist among respiratory medicine patients at a tertiary care hospital that was completely devoid of clinical pharmacy related activities. Main objectives of the study were focused upon four areas of drug therapy management viz., indication, effectiveness, safety and compliance.

Method: A prospective, interventional, cohort study carried out at Internal and Pulmonary Medicine ward of a 750 bedded premier tertiary care hospital of the region that was completely devoid of any clinical pharmacy related set-up or activities at the time of this study. A total of 182 patients of all age groups, of which 121 (66.48 %) were males and 61 (33.51 %) were females, with respiratory disorders admitted to the Internal and Pulmonary Medicine ward of a tertiary care hospital over a period of 9 months. Medication use data was collected on daily basis and reviewed by the pharmacy practitioner. Drug-related needs and problems of patients were assessed using set criteria. Pharmaceutical care plans were formulated and medication interventions proposed as and when required to the medical practitioners. Outcome measures: pharmaceutical care services, drug-related problems, clinical pharmacist led interventions, therapy outcomes.

Results: A total of 388 DRPs, were recorded among 182 patients with an average of 2.13 DRPs per patient in this study wherein a total of 258 interventions were made by the pharmacy practitioner in a total of 182 patients with an average of 1.41 interventions per patient. A total of 177 patients were offered patient counseling services with considerable benefits in terms of improved patient satisfaction and compliance. Feedback obtained from doctors, nurses and pharmacists of the study unit regarding pharmaceutical care services offered by the pharmacy practitioner was highly satisfactory.

Conclusions: This study underscores the need for initiation of clinical pharmacy services in all major hospitals of the region and the involvement of trained clinical pharmacists in direct patient care. This type of interdisciplinary and inclusive approach shall go a long way towards improving healthcare services to patients and modifying their health related quality of life.

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P075

Drug Utilization Patterns and Patient Compliance of Statins in Patients of Diabetes Mellitus at a Tertiary Care Hospital

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Introduction: WHO has estimated in its World Medicines Situation Report 21 that half of medicines throughout the world are inappropriately prescribed, dispensed or used. A number of separate studies have reported that millions of dollars are being wasted when drugs are inappropriately used, and at the same time putting the patient to unnecessary risks of morbidity and mortality. Several studies have revealed that DUE studies improve prescribing practices, quality of life, use of medications, decrease healthcare costs and promote better utilization of scarce healthcare resources. Overall objectives of DUE are to achieve quality use of medicines and improve patient care by ensuring appropriate, safe and cost-effective drug therapy.

Aim: Main objective of this study was to evaluate the drug utilization patterns of statin therapy in diabetic patients as well as patient compliance towards the prescribed statins at a tertiary care hospital.

Method: Prospective, cross-sectional, observational study using a structured data collection form was used.

Results: Out of 120 patients, a total of 57 patients had been prescribed a statin. Statin prescription was restricted to Atorvastatin and Rosuvastatin only with Atorvastatin being prescribed in 50.87 % patients and Rosuvastatin in 49.11 % patients. Average per month expenditure of statins varied considerably among different brands of statins prescribed. There was 1061 % variation between the estimated monthly expenditure of lowest cost generic available and highest cost branded form of Atorvastatin 10 mg prescribed and a variation of 841.3 % in case of Atorvastatin 20 mg. Out of 57 patients, a total of 23 (40.35 %) patients were highly adherent to their prescribed statin, while as 27 (47.36 %) patients showed medium adherence and 07 (12.28 %) patients were poorly adherent to the prescribed statins. Reasons cited by patients for low adherence to statins included non-affordability (23.52 %), lack of proper education (41.17 %), polypharmacy (20.58 %) and myopathy (14.70 %).

Conclusions: Statin use in the study population was found to be in consonance with the established standards of care. There is a considerable need for prescribing quality generics or low cost brands owing to high cost of branded statins that often results in patient non-compliance. Patient counseling and education is an important area that needs considerable attention.

P076

Adverse Drug Reactions of Antibiotics in France, 2005–2014

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Introduction: Antibiotics are largely used in France: in 2014, use was 29.2 Defined Daily Doses/1000 inhabitants/day in the community and 2.2 in the hospital sector, higher than the EU means of 21.6 and 2.0, respectively. It is thus important to analyse adverse drug reactions (ADRs), as inappropriate use can induce adverse drug reactions (ADRs) representing a burden in terms of public health.
Aim: To describe ADR cases for antibiotics reported to the French Pharmacovigilance system over a 10-year period.
Method: For this retrospective study of antibiotic ADRs reported in France, we used the French Pharmacovigilance database. All ADR cases for antibiotics for systemic use (ATC code J01) reported between 2005 and 2014 were included. Characteristics of patients, antibiotics involved, type of ADRs sorted with MedDRA by system-organ classes (SOC) and preferred terms (PT) and seriousness of cases were reviewed. These data were put in perspective with sale data and safety information issued by the French medicines agency.
Results: Out of 39,755 case reports over the 10-year period, 57.8 % were serious. The median age of patients was 50 years (range 0–115) and the sex ratio was 84.8. The SOC most frequently involved were Skin and subcutaneous tissue disorders (17,380 adverse effects), Blood and lymphatic system disorders (6371) and General disorders and administration site conditions (4377). Antibiotics most frequently involved were Beta-lactam antibacterial, penicillin (J01C) (14,235), other beta-lactam antibacterials (J01D), mainly represented by cephalosporins (8366) and Quinolones antibacterials (J01M) (7809). During the study period, the number of reported ADR cases increased regularly and doubled between 2005 (n = 2,853) and 2014 (n = 5,662). Seriousness also increased from around 50 % in 2005–2006 to around 60 % in 2011–2014. Meanwhile, antibiotic sales slightly increased. The French medicines agency issued safety alerts on antibiotics such as: linezolide and neuropathy (2006), telithromycine and hepatitis (2006), moxifloxacin, fulminant hepatitis and toxic epidermal necrolysis (2008), cefepime and neurologic effects in case of renal failure (2014), etc.
Conclusions: The increase in the number and the seriousness of cases for antibiotics followed the general trends in spontaneous reporting observed in France for all medicines during the same period; this could be explained by a lower underreporting, perhaps in part due to safety alerts of the French medicines agency and an increase of the French population. Reducing the inappropriate use of antibiotics could lead to a decrease in the number of ADR cases.

P078

Impact of Integrating Pharmacovigilance in Moroccan Tuberculosis Control Programme

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Introduction: Public Health programs are well structured but often represent a favorable model for the development of adverse events (AEs) by irrational use of drugs.
Aim: The objective of this work is to demonstrate the interest of integrating Pharmacovigilance in Moroccan Tuberculosis Control Programme (MTCP).
Design and data collection: Integration of Pharmacovigilance in MTCP was conducted in October 2012 with the Global Fund support. Using spontaneous reporting after Pharmacovigilance sensitization sessions. Comparison of spontaneous reports before and after the integration of Pharmacovigilance in MTCP (January 2010–October 2012/October 2012–April 2013) using SPSS Version 10.0 for data analysis. Detection of Moroccan signals using the information component (IC) of VigiMine. Development of actions risk minimization.
Results: As reports indicators: the average number of spontaneous reports increased from 3.6 to 37.4 cases/month (10.3 times, $p < 10^{-3}$). As AEs indicators: the average age was 40.7 ± 17.5 years, the sex ratio was 0.8. Hepatic reactions (32.7 %) predominated during the first period while skin reactions (22.7 %) were in second period ($p = 10^{-4}$), 40.9 % of cases in the first period were serious against 23.5 % in second period (p = 0.003), 4.7 % of cases in the first period have been fatal against 0.7 % in second period ($p < 10^{-4}$). Five signals were generated (hepatic enzyme increase IC = 2.77, arthralgia IC = 2.64, pruritus IC = 1.84, acne IC = 1.54, hepatitis IC = 1.22). As action of risk minimization, a national procedure of TB hepatotoxicity was developed.
Conclusion: The integration of Pharmacovigilance in Moroccan Tuberculosis Control Programme allowed rapid identification of events that are likely to affect adherence to treatment and determination new signals of antituberculosis drugs.

P079

How to Ensure Your Pharmacovigilance Services Can Continue to Support Your Products at Your Portfolio

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Introduction: How does a growing company ensure that the Pharmacovigilance (PV) functions are sufficiently flexible to maintain high quality as their workloads increase when new products come on-line? How does a growing company ensure it has flexible functions that are able to provide the latest legal requirements regarding patient safety and PV? This case study will show you how one company achieved these two objectives.
Method: Background: In 2004, PPD began case processing for a large biotechnology company with four staff in the United States (US) at a volume of ~300 US cases per month for a single product. Expansion occurred in 2007 to include case processing for an additional product along with medical review services. In 2012, as a result of additional scope/significant volume expansion including case processing for additional products along with ex-US cases and literature surveillance for two

products, a cost effective solution was recommended to add a case processing team in both PPD's Bulgaria and Philippines office. Currently, there are 189 staff on the project across three locations, (US, Bulgaria and Philippines) processing ~+20,000 cases/month. Literature surveillance responsibilities further expanded to four products in 2013.

Results: Solution: Global positioning of the team created a flexible resource model, such as having a percentage of the Philippines team overlap the US time zone and adhere to a US holiday calendar. This solution allowed for scalability as well as on-demand requests of additional work. Certified trainers were designated within each region to maximize training schedules and ensure consistency. Furthermore, specialized case processing teams were developed for certain products/case types that had specific and/or complex requirements. This enabled the broader case processing team to focus on more common cases; thus, maintaining productivity and quality, while also ensuring the specialized teams met the demands for those certain products/case types. Effective governance framework and project management ensured deliverables were achieved on-time with consistency and high-quality. Throughout the course of the program, multiple process optimizations were reviewed under the governance framework and implemented, which provided additional cost savings. This case study demonstrates how the project was planned, implement and monitored to ensure high quality timely deliverables.

Conclusions: A cost-effective solution, while delivering high-quality deliverable s on-time was achieved by meeting the client's expectations of providing a flexible/scalable solution to meet their demands. As a result of this successful relationship, PPD PV was awarded a 5-year partnership, which included the additional service of submissions of all safety reports.

P080

Pharmvigill© Mobile App for Pharmacovigilance Programmes: Easy and Efficient Way of Assessment of Adverse Drug Reactions

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Introduction: Adverse drug reactions (ADRs) are becoming a serious health problem across the globe. They incur huge mortality, morbidity and monetary burdens on the global healthcare system [1]. The serious ADRs are now recognised as fourth leading cause of death in USA [2]. Early identification and analysis of ADRs is imperative in decreasing the burden of (at least) preventable ADRs [3,4]. Information Technology can provide an efficient alternative tool to detect and analyse an ADR using smart phone based mobile app.

Aim: To design a mobile app for analysis of ADRs in dynamic clinical setting.

Methods: We combined five different ADR analysis scales consisting more than 56 test items into a single questionnaire consisting of 16 questions. The scales incorporates (1) WHO-UMC Causality Assessment Scale, (2) Naranjo's Causality Assessment Scale, (3) CIOMS Predictability Scale, (4) Hartwing's Severity Scale and (5) Modified Schumock and Thronton's Preventability Scale. Algorithms were written and mobile app was designed using Android Studio with Eclipse plug-in along with SDK tools and manager. The app runs on android based Operating System of version 2.1 or higher. The app was provisionally tested by 12 doctors and ADR monitoring Centre staff.

Results: The app was easy to use. It significantly decreased the effective time in completing the assessment of a clinical case file using five scales from 4.78 min to just 54 s with accuracy of almost 100 %.

Conclusion: Pharmvigill© ADR Analyser mobile app can be an effective alternative to manual ADR analysis in clinical setting and can become an important tool in strengthening the WHO-UMC Pharmacovigilance programmes.

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P081

21st Century Pharmacovigilance: Intuition, Science, and the Role of Artificial Intelligence

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Introduction: In a world increasingly driven by social media, *more* real time data from individual consumers is not always synonymous with *better* information. Despite the frustrating increase in the signals-to-noise ratio, social media is becoming an ever-more significant source of potentially valuable pharmacovigilance information. Social media efforts have, in some important and measurable circumstances, revolutionized safety concerns for rare diseases and adverse drug reactions.

Methods: In many respects these efforts by both U.S. and E.U. regulatory agencies suggest 21st century pharmacovigilance should be based on the concept of *Design Thinking* which requires intense cross examination of the filters that have been employed in defining a problem and to revise the opportunity before embarking on its creation and execution.

Observations: Design thinking requires cross-functional insight into each problem by varied perspectives as well as constant and relentless questioning. Unlike critical thinking, which is a process of *analysis*, according to Robert Jamison, Ph.D., professor of anesthesia and psychiatry at Harvard Medical School and pain psychologist with Brigham and Women's Hospital, mobile medicine is helping chronic pain patients cope with and manage their condition thanks to new smartphone apps, which can track patients from a distance and monitor pain, mood, physical activity, drug side effects, and treatment compliance. And according to a new report just issued by the Center for Technology and Aging, medical optimization ("med-ops") via information technology is an important element to improving medication-related errors and improving medication adherence among older adults. The report says "widespread use" of technology aimed at this population could save thousands of lives and billions of dollars.

Conclusion: The Institute of Medicine reports that more than 2 million serious adverse drug events and about 100,000 deaths occur annually due to medication use problems. The New England Healthcare Institute estimates that $290 billion in healthcare expenditures could be avoided if medication adherence were improved. The report addresses three areas of opportunity for medication optimization: reconciliation, adherence and monitoring. It describes the technologies being used or under development within the three areas along with an assessment of their pros, cons, market stage and economics. As David Lindeman, Ph.D., director of the Center for Technology and Aging, commented, "… effective tools and technologies already exist to greatly reduce these problems," said Lindeman. "Ultimately, medication optimization technologies can lead to significant improvements in the cost and quality of care for older adults."

P082

Considerations in Pharmacovigilance of Biosimilars

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Introduction: Despite the fact that the biosimilar and reference drug can show similar efficacy, the biosimilar may exhibit different safety profile in terms of nature, seriousness or incidence of adverse reactions. Also, since no two biologic medicines are identical, post-approval safety monitoring will be critical to detect potential differences in safety signals between a biosimilar, its reference product, and other biosimilars. The effect of such biosimilars on diverse patient populations with respect to the dosage and duration of therapy needs to be closely monitored.
Methods: Due to these reasons, biosimilars are required to undergo same Pharmacovigilance regulations as its reference product. Unlike the generic drugs for small molecules, the biosimilars will undergo stringent regulatory processes. As the biosimilars can be manufactured in multiple different ways and have human/animal origin, they can yield to the formation of biological product with similar efficacy but varied adverse effects to the reference. Thus, unlike small molecule generics, a biosimilar approval requires clinical studies to ensure that small manufacturing changes have not altered the therapeutic efficacy of the biological drug.
Observations: For the biosimilar specific data is limited to the comparability exercise. It is known that (small) changes in the production and purification process of biologicals can have (major) implications on their safety profile, which will mainly be reflected in an altered immunogenicity profile. It is highly expected that adverse events based on the pharmacology of the biological are similar between biosimilar and reference product. Since the manufacturing process of the reference product is proprietary knowledge, the manufacturer of the biosimilar will not be able to precisely replicate the protein product, which may influence the benefit–risk profile.
Conclusion: Post-approval safety monitoring in the USA uses two signal detection systems: spontaneous reporting systems (SRSs) and active surveillance (AS) systems. Both depend on accurate identification of the specific product(s) dispensed or administered to patients, which may be compromised when products from multiple manufacturers share common drug nomenclature or coding. For products (such as biologics) that are relatively sensitive to manufacturing conditions, *SRSs* may be useful for detection of emergent safety signals associated with changes in product quality throughout the life cycle of the medicine. *AS* systems, when used as a method to identify new safety signals, often derive multiple potential links, necessitating development of algorithms that are informed by and integrated with clinical and scientific assessment to further prove causality; the SRS and other sources may be used to prespecify potential AEs of interest.

P083

A Model to Guide Designing Risk-Proportionate Risk Minimisation and Vigilance Programs

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Introduction: The Special Interest Group (SiG) on Risk Minimisation Methods for Asian Countries was created within the International Society of Pharmacovigilance (ISoP) to exchange experience on risk minimisation tools and elaborate novel risk-proportionate methods suitable for countries with diverse health care systems, practices and resources.
Aim: After releasing open-source contents intended for risk management regulations [1], the SIG reviewed Pharmacovigilance and risk minimisation methods applied in different Asian countries e.g. (a) the Early Postmarketing Vigilance Phase (EPPV) applicable in Japan for the first 6 months of launch of any new product or indication, combining proper use enforcement and ICSR collection; (b) a pilot performed in Indonesia adapting the EPPV concept to a longer duration; (c) The Safety Management Program (SMP) applied in Thailand for any new product, which implies restricting access to the product for 2 years or more; (d) adapting components of US REMS and educational risk minimisation contents from the EU RMP.
Method: The above review and subsequent analysis resulted in designing a multiple-component concept aimed to guide creating an array of Risk Minimisation and Vigilance Programs (RMVPs) following CIOMS IX principles [2]. This concept includes a simple risk scoring considered for selecting the methods and tools to be applied in RMVPs intended for specific products in specific countries.
Results: To elaborate the RMVP model, especially the risk scoring and tool selection methods the SiG composed of Pharmacovigilance professionals of Academic, Regulatory and Industry background from Asia, Europe and North America, was extended in order to constitute an panel of experts operating according to a Delphi methodology following a process aimed to reach consensus in three rounds of questions. Feedback from ten panel members is required for proceeding to the next step.
Conclusions: In this model, criteria and weights are proposed to guide selecting those methods and tool in a risk-proportionate manner, taking into account the relevance, feasibility and acceptable burden in specific countries. To make it practical, methods and tools are categorised according to six components: (a) structured ICSR collection, (b) elaborate educational contents, (c) enforce HCP education, (d) enforce patient education, (e) product access restriction, and (f) additional data collection. For the above components, novel methods using Applications for portable devices (Apps) are being developed to take advantage from the fast deployment of smartphones operating artificial intelligence capable of bringing educational risk minimisation and ICSR collection into the hands of HCPs and increasingly empowered patients.

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P084

Medication Errors: Relevance to Pharmacovigilance

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The scope of pharmacovigilance has expanded from 'the study of the safety of marketed drugs…' [1] to 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem' [2]. A medication error—'an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient' [3,4]—is undoubtedly a medicine-related problem and falls explicitly within the new definition of pharmacovigilance. Risk management planning, introduced as part of the licensing process in the USA [5] and Europe [6], provides an opportunity to examine potential hazards and assess their occurrence prospectively at all stages of drug development. The European experience includes errors or potential errors arising from confusion of routes of administration (e.g. benzydamine, bortezomib); unexpected or non-standard dosing schedules (e.g. amphotericin, methotrexate); novel preparations of previously marketed drugs (e.g. deferasirox, insulin, olanzapine); unusual volumes for administration (e.g. romiplostim); and complex infusion regimens (e.g. tocilizumab) [7–10]. One challenge facing regulators is to anticipate errors that are likely to occur with products that have yet to be licensed. EMA has published draft guidance, which should help [11]. So too could simulation testing of proposed regimens to determine the weak points where errors are likely to occur. However, many errors occur as a consequence of the confusion of names or appearances of medicines, and while there are protocols for avoiding look-alike and sound-alike errors, these are imperfect [12]. Regulators and applicants for market authorizations might be thought to have failed if they do not show due diligence in systematically assessing the risks of errors before marketing.

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P085

An Observational Study to Analyse the Adverse Drug Reactions Among the Elderly at a Tertiary Care Hospital

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Introduction: Adverse drug reactions [ADRs] are more frequently encountered in the elderly (>60 years) population. The etiology is multifactorial and often interconnected with interplay of many factors like polypharmacy, altered drug pharmacokinetic and pharmacodynamics responses, drug interactions that increase their risk for ADR, making them a vulnerable population. Hence, the present study was taken up.

Aim: To evaluate clinical pattern, causality, severity and preventability of ADR's in the elderly population and to evaluate potentially inappropriate medicines [PIM] leading to ADRs using Beer's criteria.

Method: An observational study was conducted to analyze ADRs in elderly reported from Victoria hospital attached to BMC&RI. Relevant data on patient's demographics, details of ADR's, causal drug details, outcome were collected as per CDSCO ADR reporting form during 2011–2015. Causality was assessed using WHO causality assessment scale, severity using modified Hartwig and Siegel severity scale and preventability by modified Thornton and Schumock scale. Potentially inappropriate medicines (PIM) were determined according to Beer's criteria.

Results: A total of 809 ADRs were reported during the study period, out of which 11 % were reported in elderly. Majority (86 %) were noted in the age group of 60–70 years. Dermatological (34 %) followed by GIT (24 %) system was predominantly affected due to ADR's. Maculopapular rash

(29.21 %) was the most common ADR followed by gastritis (7.86 %) and diarrhea (5.61 %). Major contribution to the ADRs was from J01 cephalosporins (22.5 %), N02 NSAID's (20.22 %) and J05 antiviral (6.7 %) of the ATC groups. 87.6 % of the ADRs were probable and 12.4 % were possible on WHO causality scale. Zidovudine induced anemia was the only severe ADR observed in the study. Others were mild (51.68 %) and moderate (44.94 %). Majority were type A (98.87 %) ADRs and probably preventable (92.1 %). In 66.29 % of cases the drug was withdrawn, dose unchanged (28 %), dose reduced (5.6 %). The odds of developing maculopapular rash was three times more with ciprofloxacin compared to ceftriaxone. According to Beer's criteria 30.33 % of drugs causing ADR were PIM with NSAID's (20.22 %) being the most common inappropriately prescribed drugs.

Conclusions: Most of the ADRs in elderly are predictable and preventable and are caused by commonly prescribed drugs like antibacterial and analgesics. Nearly one fourth of the ADRs were due to PIM which can be minimized by careful application of Beer's criteria. Minimal number of serious ADRs observed in the study highlights rational prescribing among elderly in our centre.

P086

Biosimilars in Oncology: Do They Really Behave Similar?

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Biological agents or "biologics" are widely used in oncology practice for cancer treatment and for the supportive management of treatment-related side effects. Unlike small-molecule generic drugs, exact copies of biologics are impossible to produce because these are large and highly complex molecules produced in living cells. The term "biosimilar" refers to a biological product that is highly similar to a licensed biological product (reference or originator product) with no clinically meaningful differences in terms of safety, purity, or potency. Biosimilars have the potential to provide savings to healthcare systems and to make important biological therapies widely accessible to a global population. As biosimilar mAbs begin to enter the landscape of cancer treatment, it is increasingly necessary for cancer specialists to understand the issues involved in biosimilar development to enable them to make informed decisions when integrating these drugs into their clinical practice. As biosimilars for rituximab, trastuzumab, and bevacizumab are available and many are expected to reach the market in the near future, clinicians will soon be faced with decisions to consider biosimilars as alternatives to existing reference products. The regulatory framework for the development of biosimilars is evolving on a global scale and robust efforts are being made to manufacture high-quality, safe, and effective biosimilar agents. There may be subtle differences in the chemical structure and immunogenicity compared with the reference product, which may alter the clinical response, long-term outcome or toxicity over time. Therefore, a post-marketing safety monitoring system is put in place for biologics (including biosimilars), and oncologists play a key role in documenting any adverse drug reactions. The aim of this presentation is to discuss about the biosimilar development and evaluation process, and to offer guidance on how to evaluate biosimilar data in order to make informed decisions when integrating these drugs into oncology practice. We will also review several biosimilars that are currently in development for cancer treatment including Indian guideline of similar biologics and its requirements for clinical trial.

P087

Safety in Subcontinent Soil: Perspectives on Drug Safety in Women Health

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500,000 women die annually due to pregnancy related complication, with 99 % of them in the developing world. A study suggests that more than 50 % of all maternal deaths were in only six countries in 2008 (India, Nigeria, Pakistan, Afghanistan, Ethiopia, and the Democratic Republic of the Congo) Health indicators of women health like contraceptive prevalence, minimal four antenatal visits and birth attendance by skilled person, gives us sense of urgency. On average subcontinent has 8–10/10,000 physicians and 6–16/10,000 midwives. Compounding these health woes for women are poor regulatory procedures for pharmaceutical products, counterfeits and lack of access to essential medicines putting our woman's health at a greater risk. Feminization of poverty along with domestic violence is common practice since centuries. Current paper studies if at all, the health indicators have shown any improvement in Pakistan in specific and in the region in general. Paper reviews scientific work carried out in the region for past 10 years. Only about of third of emerging world has access to essential drugs. On average the government spends only 29.7 % of total pharmaceutical expenditure; the rest is carried out by the private sector. There are 0.092/10,000 pharmacies in public sector and 67 % of pharmaceutical personnel are pharmaceutical assistants and technicians. The total licensed pharmacies are 0.43 for 10,000 per capita. Poor access to regulated and trained health workers by women leads to their approaching untrained and fake practitioners. Poor access to fertility control or family planning centers due to social cultural and religious reasons leads to unwanted pregnancies and unsafe abortion causing high morbidity and mortality among women. Unregulated fertility practices and surrogacy are emerging worries along with infanticide and foeticide. Women in Pakistan just like her subcontinent sisters have suboptimal health and social care.

P088

Safety Issues in Unani Medicine

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Introduction: Unani system of medicine (USM) also called as Greeco-Arab Medicine is an age old system since 500 B.C. that mostly utilize the drugs from plant origin. USM is based on certain basic principle that concludes that Unani Medicines (UM) are safe in use and does not cause any adverse effects. But the reality differs from this fact nowadays. In China only, where herbal medicines are widely used, there were 9854 known reported cases of adverse drug reactions in 2002 due to herbal drugs [1]. Apart from this, there are many other cases where UM are causing side effects.

Aim: Present study focuses on some issues regarding the safety issues that are arising in UM.
Method: Inspite of various literary techniques mentioned in Unani Classical literature that make even the toxic drug (Advia simmiya) safe in use, there are many cases which are reported clinically that marks a wide scope of re-check prior to the consumption of UM.
There are many factors responsible for the adverse effects caused by UM e.g. mis-identification, unprocessed drug, improper use, herb–drug interaction, missing ingredient in a compound formulation, self medication, wrong prescription, direct toxicity (dose/duration) [1], contaminated drug, improper storage, packing, etc. These are some of the issues which are pre-disposing safety concern of UM and redirect us to further confirm the Unani Drugs before their prescription.
Results: About 80 % of world population is using herbal medicine for some aspects of their primary healthcare. So, it is the need of hour to make their use safer, so as to retain their trust on herbal medicine which is a part of UM. Though, the global market is on a rise for herbal medicine; but as a health practitioner, we should prescribe the safe, effective and best quality of drug according to health economy. At present, there are misunderstanding and prejudice toward the safety of herbal medicine. So, objective understanding, neutral and fair interpretation, and publicity are warranted [2].
Conclusions: Although, all adverse effects caused by UM are due to the neglected use of basic principles of USM. But still there is a need to research on UM, re-collect the data and ensure its reliable use.
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P089

Integration of Emerging Techniques in Pharmacometabonomics and Nanodiagnostics for Personalized PHAR

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Introduction: In order to improve the quality, safety and efficacy of medical treatments, pharmacotherapeutic regimens need to be tailored in accordance with the pharmacokinetic and pharmacodynamics characteristics and personalized needs of individual patients. So far medical treatments have been based on epidemiological studies of large patient populations, without taking into account an individual's genotypic as well as phenotypic variability. As a consequence, drug therapy often fails to be curative and may on the contrary produce substantial adverse effects. As such, there is need to evolve to a more individualized approach. There is increasing recognition of the limitations of the pharmacogenomic approach, which does not take account of important epigenetic, endogenous and environmental influences, such as nutritional status, the gut microbiota, age, disease and the co- or pre-administration of other drugs.
Aim: This paper describes an alternative, conceptually new and an integrated 'Pharmaco-metabonomic plus nanodiagnostic' approach to personalizing drug treatment, which uses a combination of pre-dose metabolite profiling, nanodiagnostic point-of-care technology and chemometrics to model and predict the responses of individual subjects that will lead to a better quality of life and improved therapeutic outcome in patients.
Method: Review of published literature was conducted to search for studies involving an integrated pharmaco-metabonomic plus nanodiagnostic approach to personalizing drug treatment for improved and safer use of medicines.
Results: Results of the systematic literature review shall be presented during the conference in the form of a poster.
Conclusions: The advent of pharmaco-metabolomics is a relatively new addition to the list of tools that toxicologist can use in the drug safety assessment and discovery processes. It has several benefits when compared with conventional techniques and other 'omic' approaches. The future is likely to see the development of a number of data bases centred around this technology.
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P090

Emerging Role of Pharmacometabonomics in Risk Assessment of ADRs

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Introduction: Metabonomics involves the generation of metabolic databases, based on tissue or biofluid samples, for control animals and humans, diseased patients, animals used in drug safety testing, etc., allowing the simultaneous acquisition of multiple biochemical parameters on biological samples. Metabonomics is usually conducted on biofluids, many of which can usually be obtained non-invasively (e.g. urine) or relatively easily (e.g. blood), but other more exotic fluids such as cerebrospinal fluid, bile or seminal fluid can be used. It is also possible to use cell culture supernatants, tissue extracts and similar preparations, and in special cases, as described later, intact tissue biopsy samples.
Aim: To explore the emerging role of pharmacometabonomics in risk assessment of medicines and in promoting personalized pharmacotherapy with optimum clinical outcomes.
Method: A systematic review of published literature was conducted to assess the role and impact of pharmacometabonomic studies on risk assessment and risk communication with a view to reduce harm, maximize benefits and thereby promote improved use of medicines.
Results: Impressions gathered from the systematic review of literature and evidence in support of pharmacometabonomics in risk assessment shall be presented in a plenary talk during the conference.
Conclusions: Metabonomics is now recognized as an independent and widely used technique for evaluating the toxicity of drug candidate compounds, it has been adopted by a number of pharmaceutical companies into their drug development protocols, and has been the subject of a

number of recent conferences. Using metabonomics it is possible to identify the target organ of toxicity, derive the biochemical mechanism of the toxicity, and determine the combination of biochemical biomarkers for the onset, progression and regression of the lesion.

P091

The Pharmacovigilance Concern as Quoted in Various Chapters of Raja Nighantu

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Introduction: Pharmacovigilance is defined as 'the detection, assessment, understanding, and prevention of adverse effects of drugs or any other possible drug related problems'. Pharmacovigilance is a very basic and fundamental concept which plays an important role in assessing drug safety in any system of medicine. The concept of pharmacovigilance is not new to the Ayurveda. Ancient texts of Ayurveda clearly mentioned that, if a drug is used without the knowledge of its action, it would certainly act as the poison. To avoid such consequences, classical texts of Ayurveda describes all the possible adverse reactions to medicines when they are prepared or used inappropriately in clinical practice.
Aim: To minimize the possible risks of adverse effect by adopting various guidelines and instructions mentioned in classical text.
Method: In the present review, an attempt has been made to compile, access and analyze the cautions, contraindications and possible adverse effects caused by inappropriate administration of herbal drugs described in the book Raja Nighantu.
Results: The book includes 23 chapters among them, 10 Vargas starting from Guduchyadi to Suvrnadi Varga comprises of near about 698 drugs of different herbal and mineral origin. About 230 drugs have been found to be reported for their possible side effects, if consumed wrongly or against regular protocol. Hence, a person who is well versed with Ayurveda fundamental principles should advice the useof these drugs taking all these factors into consideration.
Conclusions: The present review reports the possible adverse effects due to improper administration of certain drugs and dietetic items. These mentioned possible risks of adverse effect can be minimized by adopting various guidelines and instructions mentioned in classical text.

P092

Monitoring of Adverse Drug Reaction in Unani Medicine

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Introduction: To protect from the undesirable effects, Unani physicians had greatly emphasized on a proper reasoning in the method of preparation of drugs, including a rationale combination of various ingredients, method of administration, various preservatives, indications and contraindications in different situations and adverse drug effect profile such as adverse drug–drug or food–drug interaction. Moreover the process of Tadbeer (Detoxification) was employed during manufacturing to reduce the adverse drug reaction in Unani Medicine. There is possibility of adverse effects on the use of Unani medicines owing to adulteration, substandard quality of drugs and improper dosing schedules.
Aim: To highlight the measures to reduce and/or remove the toxic effects produced by unani drugs during manufacturing process.
Method: It is popular misconception that Unani drugs are devoid of adverse reactions, whereas many harmful effects produced by the drugs have been mentioned in the classical literatures of ancient origin. Unani physicians took all remarkable precautionary measures from their processing level that is why they do not exhibit as much adverse effects as are producing by modern medicine.
Results: Since unani medicine uses some metallic and gemstone preparations in the forms of kushtajat and khamirajaat and many poisonous drugs like kuchla, opium, arsenic, lead and mercury have also been used in polyherbomineral formulations that may produce a severe hazardous effects when they are given injudiciously, therefore it is the need of hour to evaluate the safety standard of these drugs as well as to monitor adverse reaction of unani drugs on scientific lines.
Conclusions: Hence Pharmacovigilance is as important in Unani Medicine as in allopathic system of treatment. In the present paper the future challenges related with monitoring of ADRs in Unani Medicine will be discussed.
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P093

Evaluation of Drug Utilization Pattern in Patients with Renal Impairment at a Tertiary Care Hospital

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Introduction: Drug utilization is defined as "the prescribing, dispensing, administering, and ingesting of drugs". Drug utilization Evaluation (DUE) is defined as an ongoing, structured, systematic, criteria-based and authorized review of physician prescribing, pharmacist dispensing and patient use of medications. This study model was designed as an attempt to evaluate the prescribing practices and utilization patterns in renal impairment patients. Furthermore there is paucity of published literature on drug usage in Kashmiri patients with renal impairment.
Aim: To identify patients with renal impairment and evaluate drug utilization patterns among them at a tertiary care hospital in accordance with methodology devised by WHO [1] and validated by American Society of Health-System Pharmacists [2].
Method: Present research work was carried out at two in-patient wards of General Medicine department of a Srinagar-based tertiary care hospital. Renal impairment patients admitted to two in-patient wards of General Medicine were categorized into two groups—those having Chronic Kidney Disease (CKD) and those with Acute Kidney Injury (AKI). A total of

150 patients were included in the study as per the inclusion criteria which consisted of 48 chronic kidney disease patients and 102 acute kidney injury patients.

Results: Among the CKD population, 42 (87.5 %) patients were hypertensive and 30 (62.5 %) patients were diabetic whereas among AKI population, 75 (73.52 %) patients were hypertensive and 17 (16.66 %) were diabetic, making hypertension (78 %) the most common co-morbidity. Other parameters like risk factor assessment, cost effective analysis, medication adherence, drug prescribing patterns, WHO tool indicators are discussed in detail.

Conclusions: Drug utilization evaluation studies are the first step towards ensuring rational use of medicines since by virtue of these studies gaps and barriers in rational use can be ascertained that in turn could be effectively used to direct policy measures towards their improved use. Therefore similar studies need to be replicated in all wards, hospitals and disease conditions so that optimum use of resources and effective utilization of drugs as per established guidelines could be ensured and therapeutic outcomes maximized. This study recommends regular DUE studies in all wards of the study hospital.

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P094

Hot Topics Worldwide for Women's Medicines

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Controversy still continues about impact of medicines on women of reproductive age and resulting access to new medicines. This can range from reluctance to evaluate Zika virus vaccine to a series of epidemiological studies suggesting signals of harm such as for oral fluconazole and pregabalin. Pregnancy and teratogens was the main theme of a joint ISoP-ENTIS meeting and the salient conclusions from this meeting will be presented. Even when we know about teratogenic risks of medicines such as isotretinoin, there remains evidence of poor control of this risk. Using safety engineering, research is ongoing to develop a system model for controlling this risk. Treatment of the menopause continues to be evaluated and warnings issued about hazards of "bioidentical hormone therapy". All this suggest that we need to better customise our approach to managing the risk of medicines for women.

P095

Medication Errors vs. Medical Negligence: Whose Responsibility

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Medication errors pose a serious problem to modern healthcare systems. Medication errors can occur in the prescribing, dispensing or administration of a drug, irrespective of whether or not such errors lead to adverse consequences. Chemotherapy drugs used in oncology practice present special dangers regarding medication errors because: (a) many drugs have a narrow therapeutic index; (b) are toxic even at therapeutic dosages; (c) chemotherapy regimens are highly complex; and (d) cancer patients are a vulnerable population with little tolerance. This suggests that cancer patients may be severely affected by medication errors. Prescribing errors that can occur in oncology, which are supported in the literature, include under dosing, overdosing, prescribing wrong drug, choosing wrong dose frequency, omitting a drug or dose, neglecting to add premedication or supportive care medication. In a survey of 186 oncology nurses, 63 % said chemotherapy errors had occurred in their workplace. In a study done by Serrano-Fabiá et al., 20.9 medication errors were detected per 1000 patient-days. In a comparative analysis involving several departments in Israel, the highest medication error rate was found in haemato-oncology (2.48 errors/100 patient days), followed by intensive care (0.82/100 patient days). Medication errors have also been observed in paediatric oncology. Medication errors affected nearly one fourth of the children receiving oral chemotherapy for acute lymphoblastic leukemia in Indian study. Another Indian study evaluated infusion chemotherapy among pediatric inpatients. A total of 205 observations were made and 23 (13.6 %) errors recorded. Educating and training all healthcare providers is essential, ensuring careful verification of prescription by attendant health professionals like pharmacists and nurses. Prescription error rate declined from 15 to 5 % after the computerized physician order entry system had been introduced. Institutions should establish dosage limits for antineoplastic agents, set up dose-verification procedures that stress multiple independent checks, and work to standardize the prescribing vocabulary. Patients are also a valuable resource to detect and intercept administration errors and to identify risky routines. All errors should be reported so that practitioners can learn from them. Clinical staff plays a vital role in the information, motivation and encouragement of patients to engage in their safety. If caregivers work together, most errors can be kept from reaching patients. All errors should be reported so that practitioners can learn from them. Each error should be reviewed by a multidisciplinary team, with the goal of system improvement. Chemotherapy-related medication-error prevention remains a priority.

P096

Pharmacovigilance Operations & Compliance Challenges

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Introduction: Pharmacovigilance is a necessary domain for any pharmaceutical company, health authority, and for the general goodwill of the patient population. However, in today's age of increased regulatory scrutiny and increased workload demands, administering to good pharmacovigilance practice necessitates a measurable financial burden.

Aim: To discuss the known financial impacts of setting up and operating a PV center within a country, region, or company and to mitigate the expense burdens by technology and/or efficient resource management.
Method: Automations in PV processes within the safety databases, combined with lean management in operations can successfully take an overwhelming operational situation to a manageable one, poised for future growth.
Results: Anecdotal evidence will be presented depicting a before/after of large, global companies and health authorities who have embraced these automations and optimized workflow to transform their respective PV operations.
Conclusions: While organizing a PV center remains a daunting task to complete from a blank slate, there are many operational decisions that can be made to effectively mitigate the risk involved and to set up a functional center of excellence. Further, already operational PV departments can gain current and future efficiencies by adopting a mindset that embraces technological advances in safety systems and re-imagined PV workflows that gain in resources and budgetary efficiencies.
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P097

Safety and Efficacy of Metallic Preparation of Siddha Medicine

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The Siddha system of medicine is one of the ancient traditional systems of the world. Siddhars, the spirtual scientists explored the nature for the benefit of the humanity. They used Herbals, minerals and animal products as ingredients of the preparations. The ancient Achcharias of ayurveda never discussed about the speciality of the metallic preparations. The modern system of medicine has grown to a dizzy height by its experiments. It is successful in controlling diseases spreading by microbes. Nowadays because of its achievements nobody is dying of pneumonia or cholera. In the management of emergencies the role of modern medicine is unparallel. But it is struggling in managing so many protracted conditions like auto immune diseases, cancer, geriatric problems, etc. These problems are managed impressively by the metallic preparations of Siddha system of medicine. In Tamilnadu alone according to a rough estimate about 50,000 kgs of metallic preparations including Mercury, Arsenic are prepared. The existense of mercurials and arsenicals and other herbomineral compounds are a great challenge to the pharma marketing of multinationals. Infact the multinational companies spreading fears in the minds of the people against the usage of metallic system of traditional medicine. Setting aside these remarks, people are approaching Siddha physicians for many chronic elements where modern medicine fails miserably. The concept of modern pharmacology about the usage and the toxicity of metallic preparations are not complied with the practice of mineral preparations in Siddha system of medicine. The Siddhars who invented the healthy handling of mineral preparations were fully aware of the toxicity and medicinal properties of the metals. They have described the toxic nature of metals in the ancient medical texts. They have prescribed the ways and means to subdue and modify the toxic nature of metals and make it medicinally active and safe. In certain cases they treated metals with various Herbal juices. The heat application is a wonderful doctrine of Siddha pharmaceuticals. Without knowing all these factors, irrevelant remarks are passed against metallic preparations of traditional medicine. When handling medicinal preparations the caution suggested by modern pharmacologists are also considered. Siddha doctors are availing the prevailing modern lab facilities and safely administering Siddha metalic and herbo metallic preparations to treat the challenging Immuno reactive diseases and other protracted diseases. At present the Siddha practitioners are largely using gold, silver and mercurial preparations.

P098

Quality Assurance: Safety of Medicine and Role of Physicians vs Regulators/Manufacturers

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Aim: The aims of pharmacovigilance within the industry are essentially the same as those of regulatory agencies; that is to protect patients from unnecessary harm by identifying previously unrecognised drug hazards, elucidating pre-disposing factors, refuting false safety signals and quantifying risk in relation to benefit.
Method: Safety monitoring in clinical trials involves collecting adverse events, laboratory investigations and details of the clinical examination of patients. The first step is signal generation, i.e. processes that can identify possible new ADRs. Signals may be generated through four different methods: spontaneous reporting, published case reports, cohort studies and post-marketing clinical trials.
Results: Health professionals are more likely to identify and report important ADRs if they have confidence in their ability to diagnose, manage and prevent such reactions. Early detection is important, particularly in hospitals where systems for detecting ADRs and medication errors will save lives and money.
Conclusions: Pharmacovigilance in the industry will continue to grow and develop as a discipline. A further strategy for integrating pharmacovigilance into clinical practice is the creation of open lines of communication and broader collaboration between health professionals and National Centres.

P099

Pharmacovigilance and Public Health Programmes in India

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Introduction: Developing countries like India are facing a major challenge in tackling the communicable diseases that are responsible for high rates of morbidity and mortality.
Aim: The purpose of this is to present the need for integrating pharmacovigilance as an essential component of public health programmes (PHPs) that use medicines in India.

Results: In developing countries PHPs are conducted by agencies and health workers with a wide variety of skills and expertise. Patients do not usually have direct contact with a physician as would be usual with PHPs in developed countries. Consequently, without good guidance and training programmes for health-care workers, patients in developing countries could be exposed to higher risks of medication error and/or preventable ADRs. In addition, factors such as literacy, nutrition and food habits in the community can have important consequences for adherence, therapeutic effectiveness and drug safety. Another widespread problem is that some medicines are counterfeit. Substandard products could result from poor manufacturing practices, unsuitable packaging, storage and distribution; or when generic drugs are produced by unregistered manufacturers.
Conclusions: Weaknesses in health-care systems and a shortage of resources lead to underdeveloped medicine control systems, unqualified health workers (with no medical background or even specific programme-related training) and poor medical services. A weak regulatory system may also fail to prevent the availability of substandard or counterfeit medicines.

P100

Occurrence of Anti-erythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin

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Background: The production of erythrocytes requires the hormone erythropoietin, which in adults is produced mainly by the kidney [1]. Subcutaneous administration of eprex (epoetin alfa) in patients with chronic kidney disease (CKD) was contraindicated in the European Union between 2002 and 2006 after increased reports of anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) [2]. Pure red blood cell aplasia (PRCA) is an uncommon, auto-immune serious disease marked by severe anemia. The sharp increase in incidence coincided with replacement human serum albumin as stabilizer by glycine and polysorbate (PS-80) in pre-filled syringes with uncoated rubber stoppers (1000–4000 and 10,000 IU strengths) which was introduced in 1998 to avoid the hypothetical risk of virus/prion transmission [2]. It has been proposed that phenol derivatives leached from rubber stopper by polysorbate 80 acted as the adjuvant and induced the production of anti-erythropoietin neutralizing antibody.
Aim: To determine the occurrence of anti erythropoietin antibodies by a validated bio-analytical method in a clinical study.
Method: Pre dose and post dose serum samples were evaluated using validated bridging ELISA method. The samples were evaluated by a three tier approach for detection and confirmation of anti-drug antibodies. The method was very sensitive and was able to detect antibodies upto 248.48ng/ml in clinical samples. Cut off value for the interpretation of sample result was determined statistically.
Result: The first tier involved primary screening of the samples for any occurrence of antibodies. Approx. 14 % samples were found to be screening positive and were further confirmed for the presence of any anti drug specific antibodies. No samples were confirmed positive for anti drug antibodies for erythropoietin.
Conclusion: Anti drug antibodies and the related complication PRCA is a rare complication with ESA (erythropoiesis stimulating agent) under consideration.
Discussion: Few PRCA cases have been reported on post marketing surveillance of uncoated stopper Eprex. Protein aggregation has been associated with product mishandling during illegal trade of epoetin alfa in Thailand. Along with the continued occurrence of PRCA in clusters, these findings suggest the involvement of an environmental factor in its pathogenesis [2].
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P101

A Look into the Contribution of Rajanighantu, an Ayurvedic Nighnatu Lexicon of 14th Century AD, Towards Drug Safety

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Introduction: Pharmacovigilance is a very basic and fundamental concept which plays an important role in assessing drug safety in any system of medicine. The concept of pharmacovigilance is not new to the Ayurveda. Ancient texts of Ayurveda clearly to avoid such consequences, classical texts of Ayurveda describes all the possible adverse reactions to medicines when they are prepared or used inappropriately in clinical practice.
Aim: In the present review, an attempt has been made to compile, access and analyze the cautions, contraindications and possible adverse effects caused by inappropriate administration of herbal drugs described in the book Raja Nighantu.
Method: In the present review, 23 chapters of Raja nighantu are reviewed critically. Among them, 10 Vargas starting from Guduchyadi to Suvrnadi Varga comprises of near about 698 drugs of different herbal and mineral origin.
Results: The book includes 23 chapters among them, 10 Vargas starting from Guduchyadi to Suvrnadi Varga comprises of near about 698 drugs of different herbal and mineral origin. About 230 drugs have been found to be reported for their possible side effects, if consumed wrongly or against regular protocol. Out of these 234 drugs 28 are reported to vitiate Vata dosha, 40 to Pitta dosha and 20 to Kapha dosha and 5 to all the three dosha, if administered inappropriately. There are 13 References where the drug is supposed to cause raktadushti (blood disorders), two to cause Shukrakshaya (decrease sperm count) and one is Punsatavghana (loss of libido) if administered without following proper treatment protocol. Hence, a person who is well versed with Ayurveda fundamental principles should advice the useof these drugs taking all these factors into consideration.
Conclusions: The present review reports the possible adverse effects due to improper administration of certain drugs and dietetic items. These mentioned possible risks of adverse effect can be minimized by adopting various guidelines and instructions mentioned in classical text.

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A Meta-Analysis Evaluating the Risk of Ophthalmic Adverse Events Associated with MEK Inhibitors

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Introduction: The inhibition of MEK, which integrates the MAPK cascade, prevents tumour proliferation [1]. Currently, trametinib and cobimetinib are the only MEK inhibitors approved for treating patients with BRAF V600 mutated melanoma [2]. Treatment with MEK inhibitors have been associated with ocular toxicity, including blurred vision and loss of visual, and serious adverse events such as serious ocular events, such as retinal vein occlusion or retinal detachment [3–5].
Aim: This meta-analysis aims to evaluate the risk of ophthalmic adverse effects associated with MEK inhibitors.
Method: A literature search was conducted in Pubmed and Cochrane Library to identify randomized clinical trials (RCTs) which have been designed to evaluate the efficacy and safety of MEK inhibitors. Overall risk of ophthalmic adverse effects, chorioretinopathy, retinal detachment, blurred vision, uveitis and eye hemorrhage were the assessed outcomes. Peto odds ratios (ORs) with the 95 % confidence intervals (CI) were pooled. Between-study heterogeneity was assessed using I^2 statistics.
Results: Thirteen RCTs were included in this meta-analysis. Overall, MEK inhibitors were associated with an increased risk of ophthalmic adverse effects (OR 2.24; 95 % CI 1.75–2.87; $p < 0.0001$; $I^2 = 86.5$ %). An increased risk was also estimated for chorioretinopathy (OR 5.44; 95 % CI 2.89–10.23; $p < 0.0001$; $I^2 = 0$ %), retinal detachment (OR 6.54; 95 % CI 3.28–13.03; $p < 0.0001$; $I^2 = 0$ %), blurred vision (OR 2.30; 95 % CI 1.50–3.54; $p < 0.0001$; $I^2 = 60.1$ %), but not for uveitis (OR 0.99; 95 % CI 0.14–7.03; $p = 0{,}991$; $I^2 = 2.9$ %) or eye hemorrhage (OR 0.72; 95 % CI 0.04–12.39; $p = 0.824$; $I^2 = 29{,}8$ %).
Conclusions: Treatment with MEK inhibitors seems to increase the risk of ophthalmic adverse effects. A need for monitoring the safety of this class of drugs exists. Regulators, clinicians and other healthcare professionals must, together, be involved in this process.
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P103

Big Data, Smart Data, Fast Data—A Paradigm Shift

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There has much recent talk of concepts like “deep learning”, “data science”, “big data”, “smart data” and “fast data”. This reflects a huge increase in interest in any potential capability improvement for the effective and rapid conversion of data to actionable insights; the promise driven by wider availability of data and increase in capability for storage and analysis. Below we describe some of the trends, illustrated with examples, which may increasingly impact routine 21st century Pharmacovigilance practice. Traditionally Pharmacovigilance was based on spontaneous report collection and analysis—systems built before the internet existed, based on paper based reporting. Epidemiological studies were primarily prospective studies on purpose built data set, and took many months to execute. With the internet, we saw the development of electronic reporting, and increasingly sophisticated electronic storage and tool based management of such data, and secondary use of existing longitudinal observational databases for studies. Now, we have vast linked distributed networks across multiple data providers. For example the US FDA’s Sentinel network covers data on over 193 million individuals, from 18 partner organisations, rapid analyses being carried out routinely across the entire network within a matter of days [1]. In developing a US national data resource, this Sentinel data system is being piloted for use by other users through the Innovation in Medical Evidence Development and Surveillance Evaluation (IMEDS) program [2,3]. Networks of collaboration across multiple countries are occurring like IMI PROTECT which conducted multiple studies across a network of databases from four European countries with even more databases for subsequent replication [4]. As well as new data streams for sharing safety concerns such as social media, there are other emerging data streams that hold promise for increasing the richness of data available for analyses. For example companies like 23andme allow consumers to get their DNA tested, and with appropriate permissions, aggregated anonymized data can be used for research [5]. Similarly video games are being tested for the record and tracking of cognition over time [6]. Technology platforms such as IBM Watson [7] are developing that use natural language processing and machine learning to reveal insights from large amounts of unstructured data, utilizing complex analytical approaches so called ‘cognitive computing’ around a range of healthcare problems. With more data than ever more, the anticipation and expectation of near real time surveillance capability and ensuing action will continue to increase. The 21st century will present many challenges for Pharmacovigilance.

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P104

Methylenetetrahydrofolate Reductase (MTHFR) Gene Polymorphism & Osteoporosis: Need An Active Solution

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Background: Osteoporosis is a common metabolic bone disorder characterized by reduced bone mass, increased skeletal fragility, micro architectural deterioration and as a consequence increased bone fracture. 300 million Indians are osteoporotic. Conventional therapy focuses only on calcium and vitamin D supplementation for osteoporosis.
Aim: To find prevalence of hyperhomocysteinemia and its impending risk for osteoporosis.
Method: Double blind randomised controlled study of 628 consecutive patients in the age group 20–70 years with 298 females and 330 males whose T-score of bone mineral density was below-1, were given 5 mg of folate and 1500 µg of mecobalamin or double placebo for 2 years. It was found that drug treated group showed 38 % decrease in plasma homocysteine levels and 76.7 % reduction in fracture incidence as compared to the placebo group being given conventional Vit D and calcium supplement.
Results: It is concluded that conventional calcium and vitamin D therapy for treating osteoporosis should be supplemented with active forms of folic acid, vitamin B6 and vitamin B12 to effectively reduce homocysteine levels in all patients as majority of patients in present study were suffering from MTHFR polymorphism.
Discussion: Methylenetetrahydro folate reductase C677T gene polymorphism has been identified as a candidate gene for osteoporosis. In the study it was found that 60 % of the population is suffering from MTHFR polymorphism. Homocysteine is converted into methionine in presence of L-methyl folate (active form of folic acid). Folic acid is converted into L-methyl folate in presence of MTHFR. So deficiency of MTHFR leads to deficiency of L-methyl folate which in turn leads of hyper homocysteinaemia, which in turn interferes with collagen cross-linking in bones leading to weak collagen matrix and osteoporosis. Similarly active form of vitamin B6 (Pyridoxine) viz pyridoxal 5′-phosphate and active form of vitamin B12 cyanocobalamin viz. methyl cobalamin converts homocysteine into cysteine and methionine respectively, thus lowering the blood homocysteine level and chances of osteoporosis. The active forms of vitamin B show higher bioavailability and bypasses the MTHFR polymorphism.
Conclusion: Active forms of vitamin (folic acid, B6 and B12) bypass MTHFR polymorphism to control plasma homocysteine levels and thus osteoporosis.

P105

Adverse Drug Reaction Monitoring at a Regional Pharmacovigilance Centre (B.P.K.I.H.S.)

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Introduction: Adverse drug reactions (ADR) are unintended drug consequences which are often preventable. ADR monitoring is the cornerstone of Pharmacovigilance. Pharmacovigilance plays an important role in rational use of drugs. This study was to observe the pattern of ADRs at Eastern Regional Pharmacovigilance Centre of Nepal, (B.P. Koirala Institute Health Sciences).
Materials and methods: It was a cross-sectional study of clinician-diagnosed ADR among patients presented to BPKIHS between July 2012 and July 2015. 150 ADRs from different departments of the Institute were collected and analyzed in the department of clinical pharmacology and Therapeutics, Regional Pharmacovigilance Centre.
Results: There were total 150 ADRs reported among patients during 3 years monitoring period. Highest percentage of ADR was collected from Department of Psychiatry (60.67 %). Maximum number of ADRs observed were due to CNS drugs (64.66 %) followed by endocrinal drugs (17.33 %) and antimicrobial drugs (12.00 %). ADR due to steroid (16.67 %), i.e., Headache, Insomnia, puffiness of face, acid peptic disorder, oral candidiasis, etc. and diverse CNS drugs related ADRs (14.66 %) e.g. dryness of mouth, sexual dysfunctions, etc. were the most common ADRs seen.
Conclusion: CNS drugs related ADRs were most commonly observed. Careful monitoring, better reporting and dedicated follow up of the patients might lead to more and better ADR detection.

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The Economic Burden of Adverse Drug Reactions Leading to and Occurring During Hospitalization

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Background: Adverse drug reactions (ADRs) are a major public health problem because they are directly related to mortality, morbidity and costs [1–3]. Due to their nature and implications, ADRs may account for a considerable number of hospitalizations, lead to poorer prognostics, and prolong hospitalization length while increasing the overall direct and indirect hospitalization-associated costs [4–6].
Objective: To analyze the comparative economic impact of hospital-acquired ADRs as well as community acquired ADRs leading to hospitalization and to characterize their associated hospitalization length and costs, incidence, prevalence, risk factors, predictability, preventability, most frequently afflicted systems and most common involved drug groups.
Methods: Systematic analysis performed on PubMed including all studies published prior to March 30th, 2016. Identified and retrieve studies (1617) were categorized as case reports, clinical studies, comparative studies, clinical trials, non-trial clinical studies, other observational studies, multicenter studies, other evaluation studies or otherwise journal articles. Only original studies in English or Portuguese language pertaining to adults and/or the elderly and reporting (as their main goal) cost resulting from ADRs/ADEs causing hospitalization and/or occurring during hospitalization were included. Studies performed on the pediatric population, those restricted to specific diseases (e.g. hypertension, chronic obstructive pulmonary disease), clinical conditions (e.g. cancer patients, trauma patients) or drug groups (e.g. antiretroviral therapy, chronic obstructive pulmonary disease), drug–drug comparative and modeling studies were all excluded from further analysis.
Results: A total of 1617 studies were retrieved, and 1483 were in human subjects. 42 % of the studies were classified as Case Reports (n = 23), Clinical studies (n = 177), Comparative Studies (n = 189), Clinical Trials (n = 146), Non-Clinical Studies (n = 8), Other Observational Studies (n = 3), Multicenter Studies (n = 62), or Other Evaluation Studies (n = 21). Few studies pertaining to hospitalization-associated ADRs and resulting cost existed and were amenable to analysis. Results were reported as mean, median and/or range and plotted as bar charts.
Conclusion: The economic burden of ADRs is not limited to the direct hospitalization-associated implications, instead having more extensive societal implications. While the most commonly prescribed drugs account for the majority of ADRs, a restricted number of medications and ADRs account for the majority of the economic burden. Therefore, identifying and targeting this limited set is of paramount importance to reduce the health-associated and economic burden resulting from ADRs.

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An Educational Intervention to Improve Nurses Reporting of Adverse Drug Reactions

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Introduction: Adverse drug reactions (ADR) are an important cause of mortality and morbidity leading to additional costs with health [1–3]. Drug safety data before commercialization is limited and incomplete, which is the reason why pharmacovigilance is important. The spontaneous ADR report system is efficient and fundamental to the safety surveillance of market medicines. Nurses can have an important role in ADR reporting due to their daily activities of drugs administration (including vaccines). However, among these professionals, there is a high rate of underreporting [4,5]. Based on the reasons proposed by Inman for underreporting ADR, it was concluded that the main obstacles to ADR reporting among nurses were indifference (the belief that a single case cannot contribute to medical knowledge) and the lack of knowledge about the pharmacovigilance system [6].
Objective: The aim of this study is to evaluate the increase of ADR reports by nurses after an educational intervention.
Methods: We performed a quasi-experimental study in nurses working in primary care in Braga district, Portugal. 113 individuals were placed in the intervention group while the control group included 590 nurses. Two educational interventions were performed to nurses working in primary care in ACES Cavado II (intervention group) that focused on the problem of adverse drug reaction, the impact on public health and spontaneous reporting. Statistical analysis were based on absolute and relative frequencies.
Results: Between January 2013 and September 2014 the Northern Pharmacovigilance Centre received 8 reports/100 nurses from the intervention group and 5 reports/100 nurses from control group.
Conclusions: The educational intervention almost double the number of reports during the study period. The 2nd intervention had more impact than the 1st one. There was no significant increase in the quality of ADR reports in the intervention group. In the 2nd intervention the number of reports increased only at the intervention day.

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Ensuring Out-Patient Safety—The Role of the Prescriber

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Introduction: Patient safety is a fundamental principle of health care. It is the absence of preventable harm to patients. The consumption of medicines is a potential source of preventable harm when patients consume the wrong medicine or the wrong quantities of the right medicine. Adverse drug events and mistaken patient identities [1] are among the more common problems with the delivery of health care. Prescribers play a vital role in what medicines are consumed by patients and their quantities. The interaction between prescribers and patients influences the decisions made during an encounter. Outpatients will usually attend a health facility for short periods. This limits their interaction with the prescriber, most often, to one encounter. The quality of interactions between prescribers and patients is instrumental in ensuring rational use of medicines, preventing avoidable adverse drug events and thereby promoting patient safety. The information given on prescription forms also informs dispensers on the medicines to be dispensed, their quantities and relevant information.
Aim: The aim of this work was to determine whether the interactions between patients and prescribers are sufficient to prevent or reduce adverse drug events and mistaken identities when it comes to consumption of medicines.
Methodology: A survey was conducted in three regions in Ghana looking into the interactions that prescribers have with consumers. The results obtained from the survey were analysed to assess the adequacy of the interaction between prescribers and consumers and the quality of information on prescription forms issued to out-patients to reduce adverse drug events and prevent mistaken identity.
Results: The survey showed that the interactions between prescribers and clients are usually not enough to prevent avoidable adverse drug events. Less than 20 % of consumers had been questioned about allergies they have, a little over 40 % were given reasons for the medications being prescribed for them and about 30 % were told the names of the medications they. Further, the information on prescription forms were inadequate to ensure that medicines are properly dispensed with adequate information.
Recommendations: There is the need to improve the quality of interactions in order to prevent avoidable adverse drug events. Prescribers must ensure that prescriptions have adequate information to ensure effective dispensing.

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Pharmacovigillance of Ayurvedic Drugs—Current Scenario

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Safety, efficacy and palatability need to be considered prior to administration of any drug. Safety is the first and most essential among these three requirements. However no drug can be called a completely safe drug in true sense. Untoward effect or adverse reaction is an integral part of drug pharmacology. Risk is always involved in any type of intrusion in human body. Concept of 'Yukta Bhaishajya' described by Caraka in Caraka Samhita, a renowned Ayurvedic classical text is noteworthy in this context. Caraka defines 'Yukta Bhaishajya' i.e. an appropriate drug as a drug which removes the disease and promotes and protects the health without causing any harm to the body. According to Kashyapa, another Ayurvedic scholar and stalwart states that administration of appropriately processed drug in appropriate dose may cause little discomfort but should remove the disease without causing major risk and permanent harm to the human body. Incidences of toxicity caused due to administration of Ayurvedic drugs containing heavy metals are being reported every now and then in the social media and some of the international journals. It has been observed that the issue is being viewed most unscientifically and with a biased attitude. Most of the reported cases appear to be the result of inappropriate handling of the patients by individuals due to the ignorance of the handler. On this background it is necessary to examine this issue scientifically. The incidences also underline the significance of pharmacovigillance of Ayruvedic drugs, which remains to be the most neglected subject today. The present paper will try to throw light on this burning issue and will try to give some solutions in this regard.

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