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International Society of Pharmacovigilance

Committed to safer use of medicines worldwide

23rd ISoP Annual Meeting "Global Perspectives on Pharmacovigilance in the Digital Age and Advanced Therapeutics" 1–5 October 2024 Montreal, Canada

ABSTRACTS

23rd ISoP Annual Meeting "Global Perspectives on Pharmacovigilance in the Digital Age and Advanced Therapeutics" 1–5 October 2024 Montreal, Canada

Dear ISoP Participant,

Welcome to the 23rd Annual Meeting of the International Society of Pharmacovigilance (ISoP) held in the stunning, lively and contemporary city of Montreal, Canada!

The theme of our conference is "Global Perspectives on Pharmacovigilance in the Digital Age and Advanced Therapeutics". This reflects not only the global reach of scientific innovation but also the advent of cutting-edge technologies that enhance the efficacy and safety of pharmaceutical products. Moreover, it underscores the strides made in personalized medicine, all of which resonate with ISoP mission. Our Scientific Committee, comprising experts in pharmacovigilance, has meticulously curated a program that places the spotlight on the application of novel technologies and the secure utilization of advanced therapeutics. This global endeavour is evidenced by the participation of members from across all five continents.

ISoP, as a collective of professionals dedicated to the rational use of medications, is committed to "fostering science and learning in pharmacovigilance in all countries." We advocate for the use of multiple sources of information, methodologies, and technologies to ensure the provision of rational use of pharmaceutical products, including devices and biologics, for the benefit of our patients. Our society welcomes anyone with an interest in enhancing medication safety, including academics, epidemiologists, regulatory agencies, clinical pharmacologists, the pharmaceutical industry, practicing clinicians, pharmacists, and other healthcare professionals. Moreover, ISoP champions networking and international collaborations globally.

This year, the program's meeting spans over 2 days of pre-conference courses followed by 2.5 days of the main conference. The pre-conference segment offers 8 courses ranging from introductory to advanced topics, including Introduction to Pharmacovigilance, Real World Evidence in Pharmacovigilance, Signal Detection and Assessment, Regulatory Framework, Evidence Medicine Tools in Safety, Introduction to Risk Management Plans, Benefit/Risk Assessment, and Practical Applications of Risk Minimization Measures.
The main conference features four plenary sessions on pivotal topics such as the Current Status of Pharmacovigilance in the Digital Era, Preparedness for Future Pandemics, Advancing Safety with New Technologies in Medical Devices and Combination Products, and The Future of Pharmacovigilance. Additionally, two regional sessions will be conducted in French and Spanish, focusing on clinical signal evaluation in pharmacovigilance and advancements and challenges in pharmacovigilance in Latin America, respectively.

With 15 parallel sessions, the conference covers a wide array of subjects, including Artificial Intelligence in Pharmacovigilance from the Industry Perspective, PV of innovative oncology-targeted therapies and immunotherapy, Digital transformation of pharmacovigilance in pregnancy, Recommendations for the use of real-world evidence to inform decision-making throughout pharmacovigilance signal management, Safety Challenges of New-Generation Therapeutics, Review of policy/ legislation/ regulation that can influence ecopharmacovigilance, Collaborative Initiatives for Safer Medications: Unifying Global Pharmacovigilance in the joint mission to prevent errors, Unleashing the potential of digitalization in empowering patient engagement, Digital tools in Pharmacovigilance and how they can be improved, Opioid Initiatives: A Global Perspective, PV Training Needs and PV Professional Certification, CIOMS Guidelines on Benefit-Risk, RWE, and Artificial Intelligence, Registries and other cohorts utilising artificial intelligence in PV: Principles and examples, Pharmacogenomics in PV, and Automation in PV, reflecting the diversity and depth of the field.

We warmly welcome you and hope that you find the meeting both enriching and enjoyable.

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International Society of Pharmacovigilance
ISoP Secretariat Ltd

140 Emmanuel Road, London SW12 0HS, UK
Tel and Fax: +44 (0)20 3256 0027
administration@isoponline.org

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ORAL PRESENTATIONS

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Exploring the Relationship Between Medication Use and Falls Among Older Patients in Peru: A Retrospective Observational Study

Teodoro Oscanoa[1,2,3], José Amado-Tineo[2,4], Silvia Leon-Curiñaupa[1], Edwin Cieza-Macedo[2,3], Roman Romero-Ortuno[5,6]

[1]Universidad de San Martin de Porres, Facultad de Medicina Humana. Centro de Investigación de Seguridad del Medicamento., Lima, Peru. [2]Universidad Nacional Mayor de San Marcos, Facultad de Medicina, Lima, Peru. [3]Geriatric Department, Hospital Nacional Guillermo Almenara, EsSalud, Lima, Peru. [4]Hospital Nacional Edgardo Rebagliati Martins, EsSalud, Lima, Peru. [5]Discipline of Medical Gerontology, Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland. [6]Global Brain Health Institute, Trinity College Dublin, Ireland, Dublin, Ireland

Introduction: In Peru, the association between falls and medications among older patients remains largely unexplored. Understanding this relationship is pivotal for enhancing geriatric care and preventing falls-related injuries in this demographic.

Aim/Objective: The aim of our retrospective observational study was to investigate the potential association between the utilization of gabapentin, benzodiazepines, antidepressants, antipsychotics, antihypertensives, proton pump inhibitors, and tramadol, and the risk of falls among older patients in Peru.

Methods: Conducted at the Geriatric Department of Almenara Hospital in Lima, our study involved reviewing Comprehensive Geriatric Assessment reports of older patients (aged > 60 years), both outpatient and hospitalized, from January 2018 to April 2022. Data extracted included the patients' history of falls in the last 12 months (yes or no), medications used, age, sex, and Charlson Comorbidity Index (CCI). A binary logistic regression model was employed to assess the risk (odds ratio: OR, with 95% confidence interval: CI) of falls associated with different medication types, while controlling for age, sex, CCI, and total number of medications used. Statistical significance was set at $p < 0.05$.

Results: Our study comprised 1225 patients, with a mean age of 78.7 $\pm$ 7.6 years and 56.2% females. In the regression model, the only independent predictors of falls were increasing age (OR 1.03, 95% CI 1.01–1.05, p = 0.001, gabapentin (OR 1.53, 95% CI 1.02–2.30, p = 0.040), and antidepressants (OR 2.61, CI 1.77–3.84, $p < 0.001$).

Conclusion: Our retrospective observational study revealed a significant association between the use of antidepressants and gabapentin and an increased risk of falls. Gabapentinoids, including gabapentin and pregabalin, are FDA-approved for various conditions, yet recent clinical guidelines have emphasized their role as adjuvant analgesics to mitigate opioid use in chronic non-cancer pain, particularly in older adults [1, 2]. Given the potential risks identified in our study, further pharmacovigilance investigations, particularly focused on gabapentinoids [3]. and antidepressants, and their relationship with falls in older individuals, are warranted.

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Literature Analysis on Immune Checkpoint Inhibitors-Related Hemophagocytic Lymphohistiocytosis

Shenao jing[1], Shengnan Qiu[2], Chenghao Li[3], Xin Huang[1]

[1]The First Affiliated Hospital of Shandong First Medical University (Shandong provincial Qianfoshan Hospital), Department of Pharmacy, Jinan, China. [2]Shandong University of Traditional Chinese Medicine, School of Pharmacy, Jinan, China. [3]Shandong University, School of Pharmacy, Jinan, China

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and hyperinflammatory syndrome. It is characterized by excessive activation of macrophages and cytotoxic lymphocytes. The specific manifestations are excessive secretion of proinflammatory cytokines, rapid tissue destruction, and multi-organ failure [1, 2]. Immune checkpoint inhibitors (ICI) exert their therapeutic effects by blocking immune escape processes and reactivating immune cells. However, uncontrolled activation of immune cells often causes excessive inflammatory reactions, making ICI a key target for inducing HLH [3]. The case reports of ICI-induced HLH are increasing currently, so it need to be taken seriously during clinical drug use.

Aim/Objective: To investigate the clinical characteristics of hemophagocytic lymphohistiocytosis (HLH) induced by immune checkpoint inhibitors (ICI).

Methods: PubMed, CNKI, Wanfang Data and VIP (up to February 2024) were retrieved to collect the case reports on HLH induced by ICI. Relevant data (gender, age, underlying disease, dosage and usage, combination of drugs, occurrence time of HLH, clinical treatment and outcome) were extracted for descriptive statistical analysis.

Results: A total of 26 articles were included, involving 28 patients (19 males and 9 females); age ranged from 33 to 85 years old, with a median age of 67.5. The most common underlying disease was lung cancer with 11 cases, followed by melanoma with 5 cases. There were 6 kinds of ICI drugs in total, including 14 cases of pembrolizumab, 7 cases of Nivolumab, 3 cases of Nivolumab combined with Ipilimumab, 2 cases of Atezolizumab, and 1 case of Toripalimab and Tislelizumab respectively. 19 patients received ICI immunotherapy alone, 6 patients received immunotherapy combined with targeted therapy, and 3 patients received immunotherapy combined with chemotherapy. The shortest time for adverse reactions to occur was 6 days after medication, and the longest was 8 months. The typical characteristics of HLH include decrease of blood cells, elevation of ferritin and increase of hemophagocytic cells. Patients often experience recurrent fever, fatigue, anorexia, and other symptoms. After treatment, 13 patients recovered, 9 patients' symptoms improved or alleviated, 1 patient's outcome was unknown, and 5 patients died. The differential diagnosis of secondary HLH is complex and is usually diagnosed by experts based on the HLH-2004 diagnostic criteria combined with clinical experience. HScore has also been developed to assist the diagnosis of HLH, currently.

Conclusion: ICI-HLH has the characteristics of difficult diagnosis and high lethality. It is necessary to strengthen the monitoring of patients' blood routine and ferritin in the clinical medication, so as to find the adverse reaction as early as possible and treat it in time.

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A Decision-Support Platform Powered by AI and Humans-in-the-Loop Boosts Efficiency and Assures Quality in FDA's Pharmacovigilance

Taxiarchis Botsis[1], Oanh Dang[2], Kory Kreimeyer[1], Jonathan Spiker[1], Suranjan De[3], Robert Ball[2]

[1]Johns Hopkins University School of Medicine, Baltimore, USA. [2]U.S. Food and Drug Administration, Silver Spring, USA. [3]U.S. Food and Drug Administration, Baltimore, USA

Introduction: The efficient application of Artificial Intelligence and Machine Learning (AI/ML) to Pharmacovigilance (PV) has gained momentum in recent years [1], while the ongoing advances in generative AI have ballooned expectations. Several regulatory agencies have released guidance and publications on the appropriate use of AI/ML in PV [2, 3]. The delivery of AI/ML solutions may also require implementing quality management systems to monitor their routine use [4].

Aim/Objective: We aimed to build a comprehensive platform incorporating several AI-based validated components and efficient features to assist PV Safety Reviewers (SRs) analyze postmarket safety surveillance reports retrieved from the FDA's Adverse Event Reporting System (FAERS).

Methods: We leveraged multi-year efforts in natural language processing, postmarket report deduplication, drug and adverse event causality assessment, and case classification to develop the Information Visualization Platform (InfoViP) in a series of FDA-funded projects starting in 2018. The previously developed Event-based Text-mining of Health Electronic Records (ETHER) system [5] processes FAERS postmarket safety report narratives, extracts clinical and temporal information, and visualizes it on the InfoViP's user interface. Combining it with structured data, InfoViP supports case deduplication and classification for assessability. Case deduplication relies on a probabilistic algorithm that detects duplicate FAERS postmarket safety reports using ETHER-extracted and structured features [6]. At the same time, another model identifies reports containing enough information to assist SRs make an informed assessment of report quality (i.e., whether a report is "assessable") [7]. InfoViP and its components were built after systematically collecting SRs' requirements in several development cycles.

Results: InfoViP's deduplication pipeline has been evaluated systematically and found to identify duplicate cases reliably, with the SRs feeling confident about its routine use. An enhanced version of this pipeline has already processed the full FAERS database and incoming daily postmarket safety reports to support the postmarket review in InfoViP and the data mining calculations in FAERS. Similarly, the best-performing ML models and the one incorporated in InfoViP achieved F1 scores above 0.85 for identifying assessable reports. InfoViP is constructed to give SRs the ability to review all predicted duplicate and assessable reports to provide human quality control.

Conclusion: We have developed a high-performing platform that can efficiently help SRs semi-automate their time-consuming tasks, such as case deduplication, and allow more time for efficient analyses. InfoViP design fully aligns with the recently discussed frameworks that require AI-based systems used in PV to keep humans in the loop for quality assurance [8].

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Strengthening Signal Detection and Causality Assessment Capacity Among National Pharmacovigilance Centre Staff: A Stepwise Pedagogical Approach for UMC's Hybrid Course

Elki Sollenbring, Nadja Jastrebova, Mónica Tarapués

UMC, Uppsala, Sweden

Introduction: Uppsala Monitoring Centre (UMC) has developed several online pharmacovigilance (PV) courses in signal detection and causality assessment to provide relevant and accessible training to national PV centre staff [1, 2]. UMC has developed a hybrid course on the analysis of national PV safety data to support those who have completed online courses.

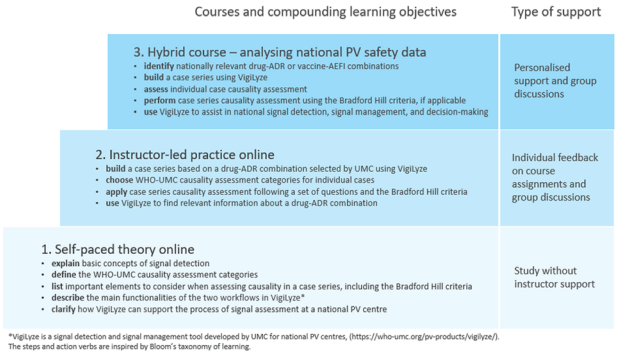
Aim/Objective: To assess a hybrid course as part of a pedagogical approach for training within signal detection and causality assessment for national PV centre staff and to evaluate participants' experiences.

Methods: The UMC learning management system (LMS) was launched in November 2020. Participant statistics from the LMS were reviewed between November 2020 and May 2022. National PV centre staff who completed theoretical and practical online courses in signal detection and causality assessment before June 2022 were invited to the hybrid course.

The hybrid course was designed for a maximum of 20 participants and divided into two parts: an online preparation and a 5-day on-site workshop. Participants identified a national drug or vaccine safety issue during the online portion. The consecutive on-site workshop focused on the in-depth analysis of the identified drug-ADR combination, including analysing the case series and applying the Bradford Hill criteria [3]. These analyses were performed individually or in groups of two participants with the support of experienced UMC instructors: four medical doctors, two pharmacists, and one data scientist. Group discussions were a valuable component of the on-site workshop. Participants completed an evaluation survey which was analysed.

Results: Out of 154 national or regional PV centre participants who had completed the online theoretical courses within signal detection and causality assessment, 72 from 36 countries had completed the practical courses and were invited to the hybrid course in 2023 (Figure 1; Steps 1–3).
Eighteen participants from twelve countries representing four World Health Organization (WHO) regions participated in the hybrid course. Twelve drug-ADR combinations were assessed in total, four of which resulted in signals, five required further investigation, and three were dismissed. The results of the evaluation demonstrated that participants found the course highly relevant, learned new skills, and planned to revise their workflow in the future.

Figure 1. Steps in the learning path with a selection of corresponding learning objectives.



Conclusion: The described learning process, beginning with theory, continuing with practical assignments delivered online, and finishing with a hybrid course, could be considered a relevant approach for strengthening the capacity building of national PV centre staff in identifying and assessing national drug safety issues.

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Association Between Major Cardiovascular Events and Esketamine: A Disproportionality Analysis in the WHO Pharmacovigilance Database

Tanguy Taillefer de Laportalière, Marianne Lepetit, Antoine Yrondi, François Montastruc

Toulouse University Hospital, Toulouse, France

Introduction: Esketamine is an enantiomer of ketamine, which was approved by the Food and Drug Administration and the European Medicines Agency for adults with treatment-resistant major depressive disorder. Due to its indirect sympathomimetic effects, esketamine exposes patients to significant increases in blood pressure after each administration. They are mediated by a systemic release of catecholamines, which inhibit the vagal nerve and the reuptake of norepinephrine and epinephrine in peripheral nerves as well as in the heart. It also has actions on calcium influx at the level of the myocardium.
Aim/Objective: Considering the known pharmacodynamic properties of esketamine and the limited cardiovascular safety data, this study aims to investigate the association between reports of Major and Cardio- and Cerebrovascular Events (MACCE) and the use of esketamine from the World Health Organization (WHO) international individual case safety report database, Vigibase®.
Methods: This study is a disproportionality analysis conducted in Vigibase®. The cases were all MACCE Individual Case Safety Reports (ICSR s) and the non-cases the other ICSRs. All the ICSRs concerning exposure to esketamine present between 01/01/2019 and 01/08/2023 were identified. Reports with esketamine in injectable form have been excluded since it used in anaesthesia. In the main analysis, tricyclic antidepressants were considered as comparator group. The association of drug-related adverse drug reaction was detected by estimating a measure of disproportionality, expressed as the reporting odds ratio (ROR).
Results: The analysis identified 37 cases of MACCE associated with esketamine. Among them, the sex ratio was 13 females and 18 males, with a median age of 54.0 years.We found 15 cases were "myocardial infarction", 22 were "cerebrovascular events" (13 cerebrovascular accident, 7 transient ischaemic attack, 1 haemorrhagic stroke, and 1 cerebral infarction) and 0 was "cardiovascular death". The main analysis found non-significant ROR for MACCE (1.17; 95% CI 0.80-1.68). While the adjusted ROR for myocardial infarction was not significantly increased (0.96; 95% CI 0.51-1.68), we found an increased risk of reporting cerebrovascular events (ROR = 1.70; 95% CI 1.01-2.76).
Conclusion: This study shows an excess risk of reporting cerebrovascular events with esketamine compared with TCAs but not for risk of reporting MACCEs. This pharmacovigilance signal for cerebrovascualr events is consistent with the pharamcodynamic properties of esketamine. It should be confirmed by other large real world studies.

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Standardized Approach Using Focus Groups to Obtain Healthcare Professionals feedback on Design and Content of Additional Risk Minimization Measures

Fadi Alanazi, Najd Alabdulrahman, Atheer Aldayel, Mariam Alghamdi, Amal Alshatri, Naser Aljaser, Fawaz Alharbi

Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Introduction: As part of its commitment to protecting and promoting public health, the Saudi Food and Drug Authority (SFDA) conducted a project to improve the current Additional Risk Minimization Measures (aRMMs). The continuous evaluation of aRMMs is a crucial component of product risk management systems. To the end of 2023, the SFDA has approved 303 aRMMs. Therefore, gathering the perceptions of healthcare professionals (HCPs) on aRMMs is very important to improve the implementation of aRMMs. Their feedback is utilized to enhance the safety of medicinal products, ensure better public health outcomes and to improve the recognized gaps in the current aRMMs.
Aim/Objective: The aim of the study is to gather feedback from HCPs on the design and content of three aRMMs (HCPs guide).
Methods: We conducted focus group meetings from April to December 2023 with HCPs in three different hospitals sin Saudi Arabia. These meetings were facilitated by Regional Pharmacovigilance Officers (RPVOs). We selected three aRMMs (HCPs guides) of targeted products (Quetiapine, Mycophenolate Mofetil, Apixaban) which were selected according to pre-defined criteria. Also, the focus group questions and a clear explanation of the project's aims and objectives provided to RPVOs through several meetings and communications. The focus group questions were carefully designed to collect data on the effectiveness, clarity, design and content of the

current aRMMs, as well as to gather suggestions for future improvement.

Results: A total of 23 HCPs participated in three focus group discussions that were conducted in three hospitals. Almost 90% of the HCPs found the materials served their purpose and provided valuable information. However, they offered key recommendations to improve the materials' content. These recommendations focused on performing regular content reviews and updates with input from multidisciplinary teams, use scientific names rather than brand names in educational content, adding more details on managing side effects, developing checklists for critical safety monitoring, implementing continuous feedback channels to gather user input, and ensuring materials focus on communicating safety risks. Participants also proposed recommendations to enhance the design of the materials. These included improving font legibility, incorporating more visual aids like tables, infographics and illustrations, and creating visually appealing and simplified materials. Other suggestions included enhancing accessibility of online materials, establishing policies and guidelines to measure aRMMs compliance and delivery in hospitals, and opening engagement channels with HCPs and patients for future initiatives.

Conclusion: The study provides valuable insights from HCPs in Saudi Arabia on enhancing aRMMs through improving content relevance, optimizing design, strengthening accessibility, and measuring compliance. Implementing these recommendations can significantly improve the effectiveness of aRMMs in promoting safe medication use and better health outcomes.

References

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Multiple Gestation Births and Perinatal Outcomes in Pregnancies Secondary to Clomiphene Citrate Treatment: A Nationwide Cohort Study

Mathilde Bourdon[1], Pietro Santulli[1], Vassilis Tsatsaris[1], Nathanaël Beeker[2], Pierre Pinson[2], Jean-Marc Treluyer[2], Laurent Chouchana[2]

[1]Université Paris Cité, Paris, France. [2]Assistance Publique - Hopitaux de Paris, Paris, France

Introduction: Clomiphene citrate (CC) is a selective estrogen modulator frequently used to induce ovulation in infertile women. Data regarding the prevalence of multiple gestation births and adverse perinatal outcomes after CC are contradicting and based on meta-analysis of small sample size studies. Multiple gestations are frequently associated with complications such as preeclampsia, premature labor, and growth restriction, which contribute to higher mortality and morbidity rates.

Aim/Objective: To assess the risk of multiple gestation birth and of selected adverse perinatal outcomes in pregnancies obtained after CC treatment.

Methods: Using the French health insurance data warehouse (SNDS) spanning 2013 to 2019, we conducted a nationwide cohort study including all pregnancies lasting more than 22 weeks of gestation, in women aged between 18-43 years. For each women, the first pregnancy during study was included. Women using assisted reproductive technology techniques were excluded. Pregnancies exposed to CC (during the period [-60days,-11days] before the beginning of the pregnancy) were 1:10 matched to unexposed pregnancies. Pregnancies exposed to CC between 12 to 2 months or less than 11 days before the beginning of the pregnancy were excluded to mitigate misclassification bias. The primary outcome was the multiple gestation birth rate.

Results: Of 3,173,013 pregnancies during study period, 32,010 (10 ‰) occurred in women exposed to clomiphene. The multiple pregnancy rate was significantly higher in CC-induced pregnancies (odd ratio 4.1, 95% CI [3.9-4.3]) such as twin pregnancies (OR 4.1, 95% CI [3.9-4.3]) and triple or more pregnancies (OR 5.1, 95% CI [3.8-7.2]), than in matched controls. Women exposed to CC presented significantly more adverse obstetrical and perinatal outcomes, including stillbirths, premature delivery threats and premature rupture of membranes. After stratification on multiple pregnancy and adjustment on confounders (history of psychiatric disease, diabetes, arterial hypertension, obesity and embryo reduction during pregnancy), women exposed to CC had a significantly higher risk of stillbirth, gestational diabetes, placenta previa, pre-eclampsia, preterm delivery and SGA in case of singleton pregnancies. Additionally, in the case of multiple pregnancies, they had a higher risk of placenta previa, preterm delivery, and SGA compared to non-exposed women. Unmeasured confouding factors might have result in indication bias, affecting some of these results.

Conclusion: Clomiphene use is strongly associated with multiple gestation births and with adverse obstetrical and perinatal outcomes, even in singleton pregnancies. These findings should provide awareness of practitioners and patients about its use. It underscores the importance of attentively monitoring follicular growth during the treatment process to avoid multiple pregnancies.

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Adverse Events of Special Interest (AESIs) Post COVID-19 Vaccination in South Africa: A Multicenter Self-Controlled Risk Interval Analysis

Kimberley Gutu[1], Alane Izu[1], Shabir Madhi[1,2,3]

[1]South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [2]Department of Science/National Research Foundation: Vaccine Preventable Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [3]African Leadership in Vaccinology Expertise (ALIVE), Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Introduction: Systematic vaccine safety surveillance is indispensable for ensuring the safety of vaccines and maintaining public trust in vaccines [1, 2]. Unfortunately, there is a paucity of post-surveillance data for COVID-19 vaccines in South Africa.

Aim/Objective: To estimate the risk of pre-defined adverse events of special interest (AESIs) with an acute onset and a short period of increased risk following immunization with a publicly available COVID-19 vaccine using a self-controlled risk interval (SCRI) study design.

Methods: A hospital-based sentinel active surveillance study was undertaken across three tertiary hospitals in Johannesburg, South Africa from September 2021 to December 2022. Patients who were admitted exhibiting symptoms indicative of any of the predetermined AESIs were evaluated for eligibility to join the study. The AESIs assessed included generalized convulsions, myocarditis, pericarditis, anaphylaxis, thrombocytopenia, thrombosis with thrombocytopenia syndrome (TTS), Guillain Barré syndrome (GBS), Miller Fisher Syndrome (MFS), Acute Disseminated encephalomyelitis (ADEM), encephalitis, and myelitis. Data was collected through an interview with the participant, as well by reviewing their medical records and results from imaging and laboratory investigations. Vaccination history was collected from the patient, and verified by the national Electronic Vaccine Data System (EVDS). Study data were collected and managed using REDCap. The data collection tools within REDCap were designed in line with the Brighton Collaboration case definitions [3] to enable the calculation of the level of certainty of the suspected diagnosis. A self-controlled risk interval analysis was done,

with cases being defined as having a level of certainty of 1 or 2, within the risk window following receipt of a COVID-19 vaccine.
Results: Out of a total of 7 168 participants that were identified as potential cases, 83.2% (n = 5 961) were enrolled. Of those, 32.4% (n = 1 930) were eligible for inclusion in the analysis, based on their vaccine status and timing of presentation relative to the vaccine history. The AESIs that had potential cases eligible for analysis were thrombocytopenia and TTS. There was no association between COVID-19 vaccination and TTS in the risk windows following the 1st and 2nd dose (risk window 1, risk ratio [rr] = 0.5 (0.06-4.11); risk window 2, rr = 0.88 (0.1-7.72)) and there was no association with thrombocytopenia (risk window 1, rr = 0.37 (0.13-1.08); risk window 2, rr = 1.16 (0.41-3.22).
Conclusion: Results from South Africa show COVID-19 vaccines did not result in an increased risk of known AESIs.
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Signal Amplification in Pharmacovigilance Using Hospital Clinical Data Warehouse: A Case Study of PCSK9 Inhibitors and Tendinopathy

Clément CHOLLE[1], Romain GRIFFIER[2,3], Virginie BRES[4], Paola SANCHEZ-PENA[1], Vianney JOUHET[2,3], Jean-Luc FAILLIE[4,5], Francesco SALVO[1,3]

[1]1. Pharmacovigilance Regional Center of Bordeaux-DROM, Medical Pharmacology Department, Hospital University of Bordeaux, Bordeaux, France. [2]2. IAM unit, Medical Information Service, Hospital University of Bordeaux, Bordeaux, France. [3]3. Inserm UMR 1219, Bordeaux Population Health Research Center, Team Ahead University of Bordeaux, Bordeaux, France. [4]4. CHU Montpellier, Department of Medical Pharmacology and Toxicology, Regional Pharmacovigilance Centre, Montpellier, France. [5]5. Desbrest Institute of Epidemiology and Public Health, INSERM, Univ Montpellier, Montpellier, France

Introduction: Signal detection is one of the main objectives of pharmacovigilance. Nevertheless, underreporting reduces the capacity of pharmacovigilance systems to find drug safety signals. The PROSPER project (PROactive amplification of Signal for Pharmacovigilance using hospital Electronic health Records) is carried out by the French pharmacovigilance network and aims to amplify pharmacovigilance signals by proactively searching for similar cases in hospital clinical data warehouses (CDW), which contain all biomedical data collected during the clinical care process of a hospital stay. A case study of PROSPER project was carried out in Bordeaux University Hospital (PROSPER-Bx).
Aim/Objective: The Bordeaux Pharmacovigilance center detected potential index case of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors related tendinopathy. The aim of this study was to assess whether querying a hospital CDW could be used to amplify this pharmacovigilance signal.
Methods: We searched for tendinopathies occurring in patients treated with PCSK9 inhibitors in the CDW of Bordeaux University Hospital, without any time or age or gender restrictions. To this end, we searched tendinopathies in unstructured data (e.g. hospitalization records or medical consultation reports) using the following keywords: "tendinitis" OR "tendinopathy" OR "Achilles tendon" and in structured data (e.g. main or associated diagnoses' coding) using ICD-10 code M76. For medication, we searched at least one prescription of PCSK9 inhibitors in the same unstructured data using the following keywords: "Praluent®" OR "alirocumab" OR "Repatha®" OR "evolocumab" OR "PCSK9" and in structured data (e.g. in-hospital prescription database) using Anatomical Therapeutic Chemical C10AX13 and C10AX14.
Results: Twenty-seven patients were initially found, with no patients retrieved using structured data only. From this initial dataset, 17 patients were excluded for the following reasons: eleven because they cited a history of tendinopathy, five because of a PCSK9 inhibitor was mentioned in the medical records but was not subsequently prescribed, and one because the actual use of PCSK9 inhibitor was not proven. Among the ten other patients, all were treated with alirocumab, which was formally suspected in three cases; the date of drug initiation or symptoms showed a tendency to be more precisely reported in suspected cases than in others. One positive dechallenge was reported.
Conclusion: Through this pilot study, we showed that unstructured data collected in hospital CDW could be useful for finding potential individual case safety reports for signal amplification. Other signals should be investigated to assess whether CDW analyses could be implemented in routine pharmacovigilance practice.
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An Improved Method for Identifying Duplicates in Global Databases of Adverse Event Reports for Medicines and Vaccines

Jim Barrett, Niklas Norén

Uppsala Monitoring Centre, Uppsala, Sweden

Introduction: In large adverse event reporting databases there can exist multiple distinct reports describing the same case, so called duplicate reports. Duplication can result from e.g., multiple independent reporters of the case, incorrectly linked versions of reports from follow-up or replication across databases (1,2). Machine learning methods are used for this problem by some organizations (3,4), however vaccine reports present specific challenges, as do settings in which the drugs and adverse event distributions deviate significantly from the database as a whole.
Aim/Objective: To develop and evaluate an improved method for identifying duplicates in databases of adverse event reports applicable to both drugs and vaccines.
Methods: A set of 1907 pairs of reports in VigiBase were annotated as either duplicates or indeterminate/non-duplicates. They were divided into subsets for training, validation, and testing, with 60%, 30% and 10% of the pairs respectively.
vigiMatch2024, which builds upon the earlier version of vigiMatch (3) in routine use for reports on drugs in VigiBase, hereafter called vigiMatch2017, introduces several improvements, including:

- A joint representation of all drug and adverse event start and end dates, and dates identified from the narrative.
- Consideration of country specific, instead of global, drug and adverse event reporting frequencies.
- Support vector machine (SVM) models (4) to balance different types of evidence of duplication.

Fixed length feature vectors representing these and other evidence for and against duplication for each pair were used to train two SVM models, one specializing in vaccine reports and the other in drug reports.

Performance of the models was assessed using reference datasets of known duplicates provided by national centers (US FDA, Netherlands LAREB, Spain AEMPS) together with the test dataset described above. The precision of the models was tested by having them make predictions for random pairs until they had each classified 100 pairs as duplicates. These were then validated by a human annotator, and the number of true positives used to compute the precision. The number of random pairs required to reach 100 predicted duplicates differed between the models and the number of true positives found per classified pair can be used as a proxy for each model's relative recall.

Results: vigiMatch2024 outperformed or equalled the performance of vigiMatch2017 for every metric. Detailed results are presented in the table below.

\Model Metric	vigiMatch2017	vigiMatch2024 Drugs	vigiMatch2024 Vaccines
Recall Dataset:			
VigiBase	0.50 (32/64)	0.67 (43/64)	0.78 (18/23)
FDA silver	0.26 (65/251)	0.48 (120/251)	n/a
FDA gold	0.29 (23/79)	0.49 (39/79)	n/a
LAREB	0.25 (13/51)	0.94 (48/51)	0.7 (7/10)
AEMPS	0.71 (5/7)	0.71 (5/7)	0 (0/1)
Precision Experiment:			
Precision	0.57 (57/100)	0.63 (63/100)	0.81 (81/100)
True Positives per Billion Classified	1.0	2.8	15.7

Conclusion: vigiMatch2024 significantly improves performance for automatically detecting duplicates in databases of adverse event reports, including for vaccines.

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Safety profile of Immune Checkpoint Inhibitors: an Updated Analysis of the Italian Spontaneous Reporting System Database

Paola Maria Cutroneo[1], Georgia Monachella[1], Ilaria Marando[1], Roberta Ranalli[2], Laura Sottosanti[2], Edoardo Spina[3]

[1]Sicilian Regional Pharmacovigilance Center, Unit of Clinical Pharmacology, University Hospital of Messina, Messina, Italy. [2]Italian Medicines Agency, Rome, Italy. [3]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Introduction: Immune checkpoint inhibitors (ICIs) enhance anti-tumor response by inhibiting immunity down-regulators like CTLA-4, PD-1, and PD-L1. They can cause various immune-related adverse events (irAEs), some of which require further investigation. The safety profiles of newly approved ICIs, including durvalumab and cemiplimab, are not fully understood. Additionally, post-marketing data needs evaluation to address safety issues, such as cardiotoxicity and other long-term implications of toxicity.

Aim/Objective: To provide an updated analysis of spontaneous ADR reports attributed to ICIs using the Italian Spontaneous Reporting System (SRS).

Methods: We selected all the ADR reports attributed to ipilimumab (CTLA-4 inhibitor), nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and cemiplimab (PD-1/PD-L1 inhibitors) in the Italian SRS from January 2011 to October 2023. Descriptive analyses have been conducted as a whole class as well as individual compounds. Reporting odds ratio was used as measure of disproportionality. ICI-related reports were compared with two reference groups, i.e. all other suspected drugs (RG1) or all other antineoplastic agents (RG2).

Results: Overall, 7035 (1,4%) reports were related to ICIs. Among these, 48.8% concerned serious ADRs. Nivolumab was indicated as a suspected drug in 3,471 (49,3%) reports, followed by pembrolizumab (N = 2,180; 31%), ipilimumab (N = 786; 11.2%), atezolizumab (N = 484; 6.9%), avelumab (N = 186; 2.6%), durvalumab (N = 173; 2.5%) and cemiplimab (N = 156; 2.2%). The majority of reports involved males (62.3%). The median age of ICI users was 68 [IQR 59-74] years. Frequencies of blood and lymphatic, endocrine, hepatobiliary, metabolism and nutrition, musculoskeletal, respiratory disorders, investigations, infections and infestations and neoplasms were significantly higher for ICIs than for RG1 ($P<0.001$). When compared with RG2, similar results were observed, except for blood and lymphatic and respiratory disorders and infections and infestations. Moreover, the reporting of renal disorders was significantly higher in ICI reports compared to RG2 ($P<0.001$).

Anti-CTLA-4 drugs were more commonly associated with gastrointestinal, hepatobiliary, and endocrine disorders, while PD-1/PD-L1 ICIs were linked to blood, lymphatic, musculoskeletal, respiratory, and general disorders. ICIs also showed disproportionate reporting with less known adverse events like ischemic heart disease, cardiac failure, optic nerve disorders, cholangitis, and malignancies, including a few cases of second primary tumors.

Conclusion: Potential safety signals were identified for specific ICIs, including ischaemic heart disease and cardiac failure (nivolumab and pembrolizumab), arrhythmias (avelumab), eye disorders (atezolizumab) and respiratory failure (durvalumab), warranting further investigation. The causality of second primary neoplasms needs careful examination to distinguish real effects from pseudo-progression or hyperprogression.

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Targeted Detection of Pharmaceutical Residues in Fish and Macroinvertebrates Around the Waste Water Treatment at Yaounde University Teaching Hospital, Cameroon

Tchadji Mayoudom Vanessa Edwige[1,2], Fossi Tankoua Olivia[3], Mbwe Mpoh Maurice[2,4], Chokwe C.[5], Ncube Somandla[6], Zebaze Togouet Serges Hubert[7], Fokunang Charles Ntungwen[1]

[1]1Department of Pharmacotoxicology & Pharmacokinetics, Faculty of Medicine and Biomedical Sciences, Yaounde, Cameroon. [2]2Cameroon Society of Pharmacovigilance, Yaounde, Cameroon. [3]3Department of Oceanography, Institute of Fisheries and Aquatic Sciences, Douala, Cameroon. [4]4Team of Research "Vigilance Médicaments Cameroun", Yaounde, Cameroon. [5]5Department of Chemistry, University of South Africa, Pretoria, South Africa. [6]6Department of Chemistry and Chemical Technology, Sefako Makgatho Health Sciences University, Ga-Rankuwa, South Africa. [7]7Department of Animal Biology and Physiology, Faculty of Sciences, Yaounde, Cameroon

Introduction: Hospital effluents are one of the main source of dissemination of pharmaceutical residues in hydro

system [1]. Worldwide, analysis of these effluents has revealed the presence of various substances [2–6]. Very few studies assessing the contamination of solid matrices by pharmaceutical residues has been carried out in Africa, specifically in Cameroon [5-7].

Aim/Objective: The aim of this study was to detect pharmaceutical residues in solid environmental matrices around the discharge of the effluent from the Yaoundé University Teaching Hospital.

Methods: Macro invertebrates and fish were collected in three sampling sites prior and after the waste water treatment plant of the Yaoundé University Teaching Hospital. Once in the laboratory, samples were freeze dried and ground. Powders were sent for analysis at the Sefako Makgatho Health Sciences University in South Africa. The analysis was carried out using an ultra-high-performance liquid chromatography coupled with a triple quadrupole tandem mass spectrometer with time-of-flight.

Results: A total of ninety-nine pharmaceutical residues related to seventeen pharmacological classes were detected in all samples of macro invertebrates (72) and Nile tilapia (55 for fish inside and 58 for fish flesh) collected. Antibiotics were the most represented (23.2%), followed by anti-inflammatory (18.2%), and anti-parasitics (9.1%). More than half (53.6%) of the drug residues detected in the fish samples belonged to the anti-inflammatory (21,71%), antihypertensive (17,67 %) and antibiotic (13,13 %) classes. The number of drug residues detected in the macroinvertebrates before the treatment plant (41) was smaller than those detected after the treatment plant (67).

Conclusion: The Yaoundé University Teaching Hospital effluent constitutes an important contamination source of the hydro system with pharmaceutical residues. This surely has an impact on solid matrices and human health that need additional research to be well understood and addressed.

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Assessing the Involvement of Pregnant Women in Reporting Adverse Events Following Vaccination in Uganda

Victoria Prudence Nambasa[1], Robert Mboizi[2], albert Figueras[3], Kirsty Ledoare[4]

[1]*African Union Development Agency, Midrand, South Africa.*
[2]*Makerere University -John Hopkins University Research collaboration [MU-JHU Care LTD, KAMPALA, Uganda.*
[3]*International Pharmacovigilance Consultant, Barcelona, Spain.*
[4]*Centre for Neonatal and Paediatric Infection, Maternal and Neonatal Vaccine Immunology Research Group, St George's, University of London, London, United Kingdom*

Introduction: Maternal vaccination protects mothers and infants from vaccine-preventable diseases [1–3]. New vaccines for GBS and RSV will soon be available in Africa. Outbreak response vaccines have already been administered to pregnant women [3-7]. However, safety data for maternal vaccines in LMICs is limited and strengthening safety surveillance systems, including the involvement of key stakeholders like vaccine recipients, is needed.

Aim/Objective: To investigate the participation of pregnant women in reporting adverse events and their perception of involvement in decision-making.

Methods: A qualitative study using interviews and focus group discussions among pregnant women and health workers in antenatal clinics in selected health facilities.

Results: Mothers were aware of the importance of maternal vaccines, especially Tetanus-Diphtheria, in protecting themselves and their newborns from infections during and after delivery.

Most women would hesitate to take vaccines when they learned about the potential side effects. In contrast, others were more open to immunisation if they received detailed information about the benefits and risks.

Many women hesitated to report adverse effects they thought to be non-serious and were unaware of the available reporting mechanisms. Reported barriers to reporting include inadequate information about what to report and how to do it, a lack of concern among healthcare providers and women about expected side effects, and unconducive patient-health worker interaction.

Pregnant women believe that they have the right to be fully informed and participate actively in decisions concerning pregnancy vaccines and medication before rollout.

Conclusion: Pregnant women need accessible information and tools to report adverse events during vaccination. It is crucial to include mothers in vaccine decisions. National Pharmacovigilance systems should actively monitor and promote reporting of events during pregnancy.

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Tinnitus Following COVID-19 Vaccinations in 2021 and 2022: a Study in a Swedish Population of 7.5 million people

Anders Sundström[1,2], Anna Baumgarten[1], Per Lindemo[1], Andreas Börjesson[1], Rickard Ljung[1]

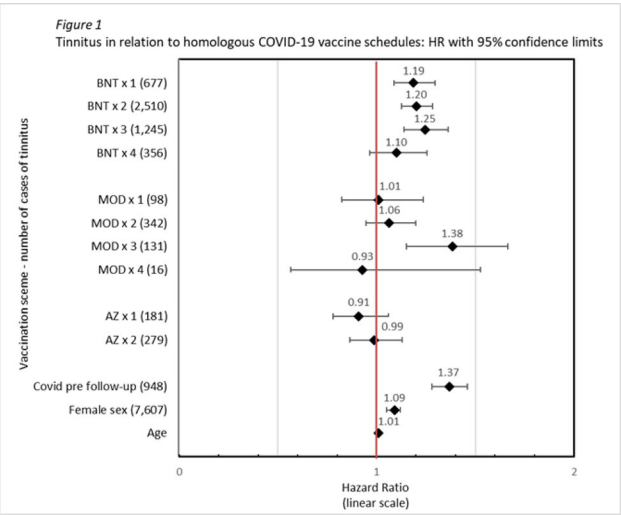
[1]Swedish Medical Products Agency, Uppsala, Sweden. [2]Uppsala University, Uppsala, Sweden

Introduction: Tinnitus following COVID-19 vaccinations is continually reported to spontaneous reporting systems: in Vigibase more than 61,000 reports are currenly (April 2024) found, and in Sweden a little over 900. Recently, an analysis in a general practice research database in Australia[1] found increased risks for tinnitus following both mRNA and adenovirus vector vaccines.

Aim/Objective: To assess the possible association between COVID-19 vaccines and a diagnosis of tinnitus using Swedish health care registers.

Methods: Within the CoVacSafe-SE register study[1] , we followed the entire Swedish population, aged 18-84 years, from start of COVID-19 vaccination on Dec 27, 2020, through Dec 31, 2022. A first diagnosis (since 2015) of tinnitus (ICD-10 H93.1) was identified in the Swedish Patient Register. Date and type of administered COVID-19 vaccination and positive COVID-19 tests were obtained from registers at the Public Health Agency of Sweden. A maximum period of 180 days after each vaccine dose was considered time at risk; when administering a subsequent dose, a new 180-days' period started. Vaccination schemes were classified as homologous schemes, 1 to 4 doses of BNT (Comirnaty®) or MOD (Spikevax ®) or 1 or 2 doses of AZ (Vaxzevria). A multi-variable Cox proportional hazards' model was fitted where individuals were followed until first diagnosis of tinnitus, a positive COVID-19 test, the fifth COVID-19 vaccination dose, emigration, death or end of follow-up.

Results: A total of 14,394 cases of tinnitus were identified, of which 7,400 (51%) within 180 days of the most recently administered dose. In Figure 1, the Hazard Ratios (HR), adjusted for age (in 1-year increments), sex and positive COVID-19 test before start of follow-up are shown together with the number of cases of tinnitus for each homologous scheme.



Homologous schemes with BNT yielded stable and in all but for dose 4 significant HR's, while 1 to 2 doses of AZ showed no association; all but one homologous MOD-scheme (MOD x 3) showed no associations. As expected, a prior diagnosis of COVID-19 was strongly associated with the outcome.

Conclusion: We observed a stable but admittedly not very strong association between homologous schemes of BNT-vaccines and tinnitus. There is, however, a distinct possibility that during the first year of the vaccination campaign these diagnoses were delayed because of limited access to health care during the first year of the pandemic, especially since the Swedish Patient Register holds diagnoses from specialized care only (open and in-patient), and not primary care. However, the lack of stable associations seen with other homologous schemes seems to contradict this.

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Consumer versus Healthcare Worker Spontaneous Reporting of Adverse Events Following Immunization in sub-Saharan Africa: Insights from Uganda's National Pharmacovigilance Database

Ronald Kiguba[1], Marble Nasasira[2], Julius Mayengo[3], Victoria Nambasa[4], Helen B. Ndagije[3]

[1]Department of Pharmacology and Therapeutics, College of Health Sciences, Makerere University, Kampala, Uganda. [2]Research and Data Centre, Child and Family Foundation, Kampala, Uganda. [3]National Pharmacovigilance Centre, National Drug Authority, Kampala, Uganda. [4]African Union Development Agency-NEPAD, Midrand, South Africa

Introduction: Understanding the patterns of reporting adverse events following immunization (AEFI) by consumers and healthcare workers is valuable for vaccine safety surveillance globally.

Aim/Objective: To compare the reporting patterns of AEFIs related to COVID-19 vaccines between consumers and healthcare workers using data from a national pharmacovigilance database in a sub-Saharan African context.

Methods: We analyzed the AEFI reports submitted to Uganda's national pharmacovigilance database, focusing on reports from consumers and healthcare workers. We conducted descriptive and comparative analyses to assess differences in reporting rates and the adverse events reported.

Results: From 10 March 2021 to 9 March 2023, the database registered 9476 AEFI reports related to COVID-19 vaccines. More than half the AEFI reports (56%, 5302/9476) were from consumers. Among healthcare workers, pharmacists accounted for the largest proportion of AEFI reports (14%, 1284/9476), while physicians submitted the fewest reports (2%, 202/9476). The median time to international registration of reports was 20 days for healthcare workers (IQR = 0, 59) and 70 days (IQR = 23,123) for consumers. One in 15 reports had serious AEFIs (6%, 614/9476). Half of the reports from physicians had serious AEFIs (50%, 102/202). Reports from pharmacists had the lowest proportion of serious AEFIs (4%, 47/1284) followed by consumers (5%, 256/5302). Most AEFI reports were singleton (53%, 4994/9476). Consumers submitted a higher proportion of singleton reports than healthcare workers [51% (2712/5302 vs. 38% (1009/2645), respectively]. A total of 17595 AEFIs

constituted the 9476 reports, mostly from consumers (57%, 9985/17595). About 16% (933/5744) of AEFIs from healthcare workers were serious versus only 6% (607/9985) from consumers. About 0.3% (50/17595) of AEFIs were fatal: 41 of the 50 fatal AEFIs were reported by healthcare workers. A total of 351 adverse events of special interest (AESI) were reported. Half of the AESI (50%, 174/351) were reported by consumers. Difficulty in breathing was the most frequently reported AESI (21%, 74/351) followed by palpitations (19%, 67/351) and erectile dysfunction (14%, 49/351). Palpitations was the most frequent AESI from consumers (24%, 41/174) and difficulty in breathing the most frequent from healthcare workers (28%, 47/165).

Conclusion: Consumers contributed significantly to AEFI reporting. Variations in reporting patterns between consumers and healthcare workers were observed, suggesting differing perspectives on vaccine safety. Although healthcare workers remain key contributors to AEFI surveillance, involving consumers in reporting could offer valuable community perspectives on vaccine safety. Thus, promoting consumer engagement in AEFI reporting is important to enhance vaccine safety monitoring in sub-Saharan Africa.

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Effectiveness of an Automated Tool for COVID-19 mRNA Vaccine ESAVIs: Data Collection Analysis and Regulatory Compliance in Mexico During Pandemic

Betty Duarte[1], Cinthya Galicia[2], Gabriela Jure[2], Yibrahan Jimenez[2], Miriam Salvador[2], Luis Zuñiga[1], Esteban Olivares[1]

[1]Pfizer, San José, Costa Rica. [2]Pfizer, Mexico City, Mexico

Introduction: On March 11, 2020, the WHO declared a Global pandemic caused by the SARs-CoV-2 virus[1]. Likewise, Pfizer, among other Pharmaceutical Companies, developed a mRNA vaccine to fight the spread of SARS-COV-2 virus. The development of such vaccine brought with it a great number of ESAVI (Events Supposedly Attributable to Vaccination or Immunization) from consumers, patients, and Health Authorities, which needed to be managed on a tight schedule to comply with Global Health Authorities and ultimately, guaranty patient safety.

Aim/Objective: Trough the creation and use of an automated tool, improve processing efficiency of unstructured data provided by the Health Authority which results in ICSR processing and submission compliance.

Methods: A macro spreadsheet tool was developed in Microsoft Excel based on the reports of the Pfizer COVID-19 vaccine, provided by the Mexican Health Authority, for the period from Jan2021 and Jul2022. The challenge found was a bulky and complex format report for data processing, however with the implementation of the macro tool was possible to improve the data processing efficiency, created an individualized source document easy to understand and optimizing the data entry accuracy and clinical analysis. Also, the tool allowed to identify potential serious reports based on MedDRA terminology for fatal, life-threating, hospitalization, injuries, procedural complications, lack of efficacy and several disease conditions resulting in an expedite case prioritization and improving the case processing compliance. This tool was validated through statistical sampling technique ANSI. Reduced inspection severity was chosen since all ICSR underwent Peer review from another qualified colleague and processing inconsistency risk is ruled out.

Results: The implementation of such tool helped reduce time spent in analysis from 24 hours to just 3 hours, or a reduction in 87% time spent prioritizing cases. It also allowed local and global teams to comply with internal processing timelines and local and Global submission This also allowed the local team to focus on what matters, having segmented information for its analysis, favoring decision making in pro of Mexican population.

Conclusion: The use of this tool did help local Team to prioritize ICSR management by reducing time spent in case analysis, resulting in local and global processing and submission compliance. The use of this tool did help local Team to prioritize ICSR management by reducing time spent in case analysis, resulting in local and global processing and submission compliance.

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POSTERS

1

Addressing Pharmacovigilance Training Gaps: Insights from a Pharmacovigilance and Drug Safety Online Training Program for Healthcare Professionals immigrating to North-America

Omar Aimer[1], Abdelkrim Cherif[1], Shams Qaend[2]

[1]*InnoVigilance, Laval, Canada.* [2]*RxCourse Institute, Mississauga, Canada*

Introduction: The United States and Canada have long been destinations for immigration, attracting professionals from various regions worldwide. In 2022, approximately 2.6 million people legally immigrated to the US, while 0.5 million moved to Canada. Amidst the COVID-19 pandemic, healthcare professionals emerged as a prominent category of workers immigrating to both countries, with some possessing experience in Drug Safety and Pharmacovigilance while others sought to enter the field.

Aim/Objective: Recognizing the lack of training and education programs in pharmacovigilance and drug safety, we developed the Qualified Professional in Pharmacovigilance and Drug Safety (QPDS) online Program. This initiative aimed to equip healthcare professionals with the necessary knowledge to join pharmacovigilance and drug safety departments in pharmaceutical companies, both locally and globally.

Methods: The QPDS Program provided comprehensive training covering the fundamentals of pharmacovigilance, local (US FDA, Health Canada), and global (ICH, EMA, PMDA, MENA, LATAM) regulations, as well as pharmacovigilance operations and quality management. From the list of program participants, we performed a search on LinkedIn to identify their background, country of origin.

Results: Analysis of the 50 program participants revealed that a 34% (17) had prior pharmacovigilance experience outside the US and Canada, while 66% (33) lacked any prior experience. Additionally, participants came from diverse educational backgrounds, with 52% (26) holding PharmD degree, 26% (13) Medicine background, 16% with education in life sciences, 4% (2) Nurses and 2 % (1) with unknown background. On the 50 participants 78% (39) were based in Canada and USA with 57% (22) newcomers and 43% (17) locals, 22% (11) overseas From all the participants Following completion of the program, a substantial number of graduates secured roles in pharmaceutical companies and obtained the QPDS certificate. This certificate facilitated their hiring process and supported their daily activities post-employment.

Conclusion: The QPDS online Program underscores the significance of pharmacovigilance training for healthcare professionals without prior experience, as well as the importance of staying updated on local regulations for experienced professionals. Given North America's status as a leading market for drug and device development, including pharmacovigilance and drug safety, such initiatives play a crucial role in preparing professionals to contribute to this dynamic field. As the demand for pharmacovigilance professionals continues to rise, programs like QPDS serve as vital resources in ensuring a skilled workforce capable of meeting the evolving needs of the pharmaceutical industry. Further analysis will be conducted to determine the career outcomes of the participants to identify the roles they joined and healthcare, academic or industry sectors.

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3

Challenges and Experiences to Establishment of a Zonal Pharmacovigilance Centre (ZPC) in a Tertiary Care Teaching University Hospital, (BSMMU), in Bangladesh

Elora Sharmin, Sheikh Ahmed

Bangabandhu Sheikh Mujib Medical university, dhaka, Bangladesh

Introduction: Pharmacovigilance revolves around monitoring and addressing Adverse Drug Reactions (ADRs) and related drug issues, contributing positively to public health. Notably, Bangladesh lacks a zonal PV center, presenting significant challenges during the establishment phase. Healthcare professionals, including clinicians, pharmacists, and nurses, are encouraged to report ADRs through designated channels.The ultimate goal is to establish a robust pharmacovigilance system in Bangladesh, addressing challenges such as limited ADR monitoring and awareness among healthcare professionals.

Aim/Objective:

1. Importance of establishing a zonal pv centre at BSMMU
2. Challenges and experiences for establishing the zonal pv centre at BSMMU.
3. Steps and future plan for establishing the zonal pv centre at BSMMU

Methods: Getting Started with a PV Center at BSMMU: Establishing a PV center at BSMMU requires coordination with national PV programs and securing governmental support. Ideally situated within the pharmacology department, the center should involve faculty from various departments.

Bringing a Reporting Culture to BSMMU: Promoting a reporting culture for ADRs in hospitals involves ensuring easy access to reporting forms, acknowledging reports promptly, providing education and awareness materials, and involving PV center staff in scientific activities.

Steps Taken to Establish a Zonal PV Center at BSMMU: to establish a zonal PV center at BSMMU include training programs, supplying ADR reporting forms, building IT-based PV systems, issuing reporting mandates, collaborating with PV organizations, and forming oversight committees.

Experiences and Challenges: insufficient data capture, knowledge gaps among healthcare professionals, reporting barriers, lack of guidelines, inadequate collaboration, and financial constraints.

Future Plans: mandating reporting, incorporating PV courses into curricula, creating databases, changing attitudes, enhancing collaboration, and utilizing IT solutions.

Results: Why a Zonal PV Center at BSMMU : a zonal PV center at BSMMU is necessary to address gaps in PV activities. Currently, only one national PV center exists in Bangladesh.

Conclusion: While PV activities in Bangladesh currently operate on a limited scale, expanding these initiatives nationwide and establishing zonal and regional centers in various medical universities and colleges are crucial steps to ensure optimal public health impact and medication safety.Furthermore, broadening stakeholder engagement to include patients, healthcare providers, academics, research institutes, and universities, along with promoting country ownership through the launch of PV programs in Bangladesh and the establishment of a zonal center at BSMMU, will further enhance the

effectiveness of the program. This collaborative approach will foster a culture of safety and accountability in medicine use, ultimately improving health outcomes for the population.

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4
Artificial intelligence detecting data integrity in pharmacovigilance

Chinmaya Mahapatra, Subas Chandra Dinda, Binaya Kumar Sethy

School of Pharmacy, The Neotia University, Sarisha, West Bengal, India

Introduction: The application of Artificial Intelligence (AI) in pharmacovigilance represents a transformative approach to ensuring data integrity within the pharmaceutical industry. Given the critical importance of accurate and reliable data for drug safety, AI technologies offer innovative solutions to detect, assess, and rectify data integrity issues. This abstract presents an overview of how AI can be utilized to enhance the quality and reliability of pharmacovigilance data, ultimately contributing to safer drug use and improved patient outcomes.

Aim/Objective: This study employs a comprehensive review of current AI technologies, including machine learning algorithms, natural language processing (NLP), and predictive analytics, to explore their application in detecting data integrity issues within pharmacovigilance databases.

Methods: The methods involve analyzing case studies and empirical research that demonstrate AI's capability to identify anomalies, inconsistencies, and patterns indicative of data integrity concerns. Additionally, the study examines the integration of AI systems with existing pharmacovigilance frameworks to assess their effectiveness in real-world scenarios.

Results: The findings reveal that AI significantly enhances the detection of data integrity issues compared to traditional manual methods. Specifically, machine learning algorithms excel in identifying outlier data points and anomalies, while NLP effectively processes and analyzes unstructured data from diverse sources for inconsistencies. Predictive analytics further enables the anticipation of potential data integrity issues, facilitating preemptive measures. Case studies illustrate successful applications of AI in pharmacovigilance, showcasing substantial improvements in data quality and reliability. The integration of AI into pharmacovigilance offers promising advancements in ensuring data integrity. However, challenges such as the need for high-quality training data, potential algorithmic bias, and ensuring human oversight are discussed. The study emphasizes the importance of a balanced approach that combines AI technologies with human expertise to achieve optimal results in maintaining data integrity. Regulatory considerations and ethical implications of AI deployment in pharmacovigilance are also explored.

Conclusion: AI technologies present a powerful tool for enhancing data integrity in pharmacovigilance, offering the potential to significantly improve drug safety monitoring and patient care. By automating the detection of data anomalies and inconsistencies, AI facilitates a more efficient and accurate assessment of pharmacovigilance data. Future research should focus on addressing the challenges associated with AI integration and exploring innovative applications of AI in drug safety analysis.

5 Global Drug Development—Current Trends, Challenges and Opportunities

Gurpreet Singh

IQVIA, Coventry, United Kingdom

Introduction:

- The entire process of developing a drug from preclinical research to marketing can take approximately 12 to 18 years and often costs well over $1 billion
- Global Top Pharmaceutical Companies based on projected R&D spending in 2026 are Roche, Johnson & Johnson, Merck & Co, Pfizer and Novartis
- The global **CRO** services **market** in terms of revenue was estimated to be worth $76.6 billion in 2023 and is poised to reach $127.3 billion by 2028

Aim/Objective: Global Drug Development Trends

- Increased Focus on Quality, Compliance and Quality Management System
- Requirements of Audit and Inspection readiness
- Process Enhancements, Changes, Improvements
- Further adoption of Technology and Tools, Database migrations
- Focus on Data Analytics and Trends
- Organisational Culture Enhancement –Focus on People Development, Training and Retention

Change Management–Mergers/Acquisitions and Integrations

Methods: Global Drug Development Challenges & Opportunities

- Requirement of skilled resources
- Retention of Talent
- People Development Needs
- Standard Operating Procedures
- Better quality and compliance
- Need for better productivity
- Adoption of Technology
- Reduce cost per transaction
- Improve Efficiency

Results:

- Understanding of the Global Drug Development Industry. The current trends, challenges and opportunities
- Four important pillars of Drug Development–People, Process, Technology and Partnerships

Consluion:

- Digital Transformation in Drug Development
- Top 10 Trends in Drug Development like **Personalized medicine, Orphan drugs for rare diseases & New clinical trial models (Decentralized Clinical Trials)**

6
The Regionalization of Pharmacovigilance in Morocco: Case of the Mohammed V Military Instruction Hospital in Rabat

Yassir Bousliman[1,2], Rachid El jaoudi[1], Mina Ait Elcadi[1]

[1]*Faculty of Medicine and Pharmacy of Rabat, Rabat, Morocco.* [2]*Mohammed V Military Instruction Hospital in Rabat, Rabat, Morocco*

Introduction: In Morocco, on January 4th, 2016, the Ministry of Health issued a circular on the reorganization of the Moroccan pharmacovigilance system, recognizing the importance of the

implementation of pharmacovigilance within hospital structures with the appointment of medical or regional pharmacovigilance pharmacists.
Aim/Objective: The objective of this work is to trace the stages of the implementation of regional hospital pharmacovigilance using the example of the Mohammed V Military Instruction Hospital (HMIMV) in Rabat.
Methods: This is a retrospective, descriptive study which relates the action plan adopted for the implementation of pharmacovigilance at the Mohammed V Military Instruction Hospital (HMIMV) in Rabat, the constraints and opportunities encountered and the progress made.
Results: The action plan began with the appointment of a pharmacovigilance leadership referent leader of the project to set up the pharmacovigilance unit (UPV) within the pharmacy center of the HMIMV, of focal points within the different services represented by doctors and nurses. Continuous awareness raising among hospital health professionals and active notification were the main levers for the successful implementation of the UPV.
The date of the circular on the regionalization of pharmacovigilance in Morocco was decisive at the level of hospitals which set up pharmacovigilance units. Thus, from 2010 to 2015 we were able to trace a few Notifications which did not exceed 10 over the Five years compared to 123, 107, 437, 109, 163 and 291 Notifications respectively in 2016, 2017, 2018, 2019, 2020 and 2021. So, the results six years before and six years after the implementation of the regionalization of pharmacovigilance in our hospital are as following: 5 notifications versus 1230 notifications respectively. Among the most serious cases notable, we cite one death from hepatic cytolysis, 08 Toxidermia including 3 Lyell Syndromes and 3 cases of Dress Syndrome, 01 Pulmonary Embolism.
Conclusion: The regionalization of pharmacovigilance through the involvement of hospitals is established and operational in Morocco. Its role and interest in promoting the pharmacovigilance system no longer needs to be demonstrated. It constitutes an essential mean of promoting the correct use of medicines and therefore guaranteeing patient safety.
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7
COVID-19 Vaccine Administration Errors or Deviations Reported to the Brazilian National Immunization Program: Descriptive Analysis, 2021-2023.

Paulo Henrique Santos Andrade[1], Leon Capovilla[1], Soniery Almeida Maciel[2], George Ricardo dos Santos[3], Krishna Mara Rodrigues Freire[2], Roberta Mendes Abreu Silva[1], Carla Dinamerica Kobayashi[1], Martha Elizabeth Brasil da Nóbrega[1], Monica Brauner de Moraes[1], Cibelle Mendes Cabral[1], Felipe Daniel Cardoso[4], Adriano Ferreira Martins[4], Jadher Percio[1]

[1]Coordenação-Geral de Farmacovigilância (CGFARM/DPNI), Brasília, Brazil. [2]Coordenação-Geral de Incorporação Científica e Imunização (CGICI/DPNI), Brasília, Brazil. [3]Núcleo de Governança da Informação (NGI/DPNI), Brasília, Brazil. [4]Programa de Treinamento em Epidemiologia Aplicada aos Serviços do Sistema Único de Saúde (CGEMSP/DEMSP), Brasília, Brazil

Introduction: Immunization errors (IEs) can result in inadequate immunological protection, adverse events, costs, inconvenience, interference with adherence to the vaccination schedule, and reduced confidence in the health care delivery system [1–3]. As far as known, this is the first work that describes the occurrence of the IE related to COVID-19 vaccines in Brazil at a national level.
Aim/Objective: To describe the IEs that occurred during the covid-19 vaccination campaign in Brazil between 2021 e 2023.
Methods: This is a descriptive study of IEs related to COVID-19 vaccines reported between January 17, 2021 and July 8, 2023 in the Brazilian pharmacovigilance information system. This study was carried out as part of the vaccine pharmacovigilance actions executed by the National Immunization Program. The primary outcome was IE and the secondary outcome was adverse event following immunization (AEFI) after IE. Data analysis calculated the IEs incidence coefficient according to the age group, vaccine, type of IE reported and AEFI reported with the IE using RStudio-4.3.1.
Results: There was 48,008 IEs reported after 545,081,792 doses administered (DA) of COVID-19 vaccines (8.80 IEs/100,000 DA), highlighting the 0 to 3 years old age group (31.49 IEs/100,000 DA), pediatric Pfizer vaccine (32.25 IEs/100,000 DA). Among the IEs, stood out "Incorrect vaccine administration" (2.19 IEs/100,000 DA) and "Inadequate age vaccine administration" (1.75 IEs/100,000 DA) (Table 1). Of the total IEs reported, 877 (1.8%) were notified with an AEFI, totalizing 0.16 cases/100,000 DA in Brazil, of this total, only one AEFI was associated with one IE. Serious events were considered very rare in this study and most of them were classified as coincidental.

Table 1 – Incidence coefficient of the main immunization errors associated with COVID-19 vaccines, by type of immunization error reported, Brazil, January 17, 2021 to July 8, 2023.

	Total	
Type of immunization error reported	N	Ic[a]
Incorrect vaccine administration	11960	2.19
Inadequate age vaccine administration	9564	1.75
Administration of expired vaccine	9486	1.74
Inadequate dose of vaccine administered	5554	1.02
Interchangeability of vaccines	3021	0.55

Ic: Incidence coefficient/100,000 doses administered. [a]Total doses administered = 545,081,792

Conclusion: IEs were more frequent among children and adolescents and among the vaccines used in this age group. This can be explained by the fact that this is a target audience for vaccination in general and due to the different guidelines for the different COVID-19 vaccines, making it possible for the wrong vaccine to be administered and used at an inappropriate age.
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8
Composition, Antioxidant Properties, and Antibacterial Preservation Potential of Algerian *Myrtus nivellei* Essential Oil

Bankaddour Zeragui[1], Noureddine Halla[1], Yasmina Benabdesslem[1], Ilyas Chikhi[2], Kadda Hachem[1]

[1]Laboratory of Biotoxicology, Pharmacognosy and Biological Valorization of Plants (LBPVBP), Faculty of Natural and Life Sciences, University of Saida - Dr Moulay Tahar, 20000 Saida, Algeria, Saida, Algeria. [2]Laboratory of Applied Chemistry (LAC),

Faculty of Sciences Technology, University of Ain Temouchent Belhadj Bouchaib, 46000 Ain Temouchent, Algeria, Ain Temouchent, Algeria

Introduction: *Myrtus nivellei* Batt. & Trab., also known as Sahara myrtle [1], is a native plant of the Algerian Sahara, mostly found in the middle region and occasionally in the north [2]. Touaregs highly respect this plant for its medical properties. When its leaves are steeped, they have therapeutic benefits against diarrhoea and blennorrhea. Crushed leaves mixed with oil or butter ointment can be used to treat skin diseases [3].
Aim/Objective: This study aimed to analyse the chemical composition of the essential oil isolated from *Myrtus nivellei* (MNEO) and evaluate its potential as a natural preservative against three common bacterial strains found in cosmetic products.
Methods: The essential oil was obtained via hydrodistillation and its composition was analysed using Gas Chromatography (GC) and Gas Chromatography-Mass Spectrometry (GC/MS). MNEO's antioxidant capacity was assessed by the DPPH test and the reducing power assay. The antibacterial properties and effectiveness of MNEO were evaluated against three common bacterial strains found in cosmetics (*Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25933, and *Staphylococcus aureus* ATCC 25923). A shampoo model was used to investigate the impact of MNEO throughout a 28-day incubation period.
Results: The analysis identified 33 compounds, accounting for 96.12% of the total composition, with 1,8-Cineole being the dominant component at 61.9%. The results indicated a 50% inhibition of DPPH at 3.04±0.21 mg/mL and a 50% decreasing power at 3.08±1.12 mg/mL. All bacterial strains were shown to be susceptible to MNEO, with *Staphylococcus aureus* being the most vulnerable (minimum inhibitory concentration = 1.5 mg/mL) and the MNEO revealed a decimal reduction equal or more than 1, which the MNEO could inhibit the growth of bacteria in shampoo by challenge test during 28 days of incubation.
Conclusion: This study shows that MNEO can successfully prevent bacterial development in shampoo formulations due to its remarkable antioxidant activity, which is mainly fueled by its high concentration of 1,8-cineole. According to these results, MNEO may be used as a natural preservative to preserve the quality of products. Its function in antimicrobial shampoos may be improved by additional research.
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9
Evaluation of LDL-C Level Post Acute Coronary Syndrome"Retrospective Cohort Study

Albatoul Alomran[1], Ghadah Aloqily[2], Mona Alsofaei[2], Sultan Aljardan[1], Saud Alqahtani[3], Hind Almodaimegh[4]

[1]King Saud bin ABDULUZIZ university for health sciences, Rayiadh, Saudi Arabia. [2]King saud university, Rayiadh, Saudi Arabia. [3]King khalid university, Abha, Saudi Arabia. [4]King Abdulaziz Cardiac Center, Rayiadh, Saudi Arabia

Introduction: Acute coronary syndrome (ACS) is a subcategory of coronary heart disease (CHD) that is characterized by decreasing blood flow and increasing oxygen demand to the heart. And it is mostly due to a plaque buildup in the coronary arteries, that is primarily caused by an accumulation of oxidized LDL in the arterial walls. (1) A high LDL-C level is a risk factor that can lead to a secondary ACS event. In order to maintain better outcomes patients with ACS should be managed with lipid-lowering therapy to achieve the guideline-targeted LDL-C level of 2.6. (2)
Aim/Objective: To evaluate the LDL-C level control in patients post ACS treated with cholesterol lowering therapy within three and six months.
•To assess the influence of age, gender, body mass index, and other comorbidities.
Methods: An observational retrospective cohort study was established in King Abdulaziz Cardiac Center KAMC.
We used the patients' electronic medical records that included all patients with acute coronary syndrome , above 18 years old with cholesterol-lowering agents who routinely followed up their LDL-C levels within 3 and 6 months.
We used simple random technique for the sample size 175 patients that met our inclusion criteria.
Results: The patients with uncontrolled LDL-C represent 58% , In addition obesity and overweight have a higher prevalent estimated 61% of our population . The levels decreased between the time of onset and 3 months with more variability ,There is no significant changes in LDL average between 3 months and 6 months . Total cholesterol is the only lipped panel decreased in a considerable amount across the span of the treatment. In a comparison between Mono and Bi therapy , Bi therapy has a significant effect on controlling LDL-C levels on ACS patients.
Conclusion: The majority of our population had an Inadequate LDL control that requires collaborative effort to reach the LDL as recommended by the guidelines.
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10
Dug-drug Interactions as a Public Health Problem: Retrospective Study of Adverse Drug Reaction Reports from the National Portuguese Pharmacovigilance System

Maria Gouveia[1], João Fernandes[2], Sandra Queiroz[2], Márcia Silva[2]

[1]Faculty of Pharmacy, Lisbon, Portugal. [2]Infarmed, Lisbon, Portugal

Introduction: According to the World Health Organisation, above 50% of patient harm is preventable, with half of this harm being attributed to medications. [1] Drug–drug interactions (DDIs) are an important cause of adverse drug reactions (ADRs), which can have a significant impact at the public health level.

Aim/Objective: Our study aims to analyze Individual Case Safety Reports (ICSRs) submitted to the National Portuguese Pharmacovigilance System and identify ADRs that may result from DDIs.
Methods: Retrospective study which analyzed ICSRs received by the Portuguese National Pharmacovigilance System in January 2023. ICSRs with more than one drug (classified as either suspect or concomitant) were selected. In order to identify potential DDIs, the Summary of Product Characteristics for each drug was consulted, as well as the UptoDate database. It was assessed whether the clinical implications of DDIs aligned with the provided description of ADRs in each ICSR.
Results: Our research retrieved a total of 727 ICSRs of which 307 contained more than one drug involved. Almost half of the ICSRs of interest, 44.6% (n = 137), were related to potential drug interactions. On the other hand, 7.2% (n = 22) of the ICSRs contained ADRs that have been described as resulting from a DDI. Approximately 32% (n = 7) of the DDIs-related ICSRs were considered serious, 9% (n = 2) of which resulted in hospitalization. Only 1 DDI-related ICSRS contained coding associated to drug interaction. Most of the DDIs identified are due to additive effects of pharmacological class or similar indications involving central nervous system depressants, immunosuppressive medications, hypotensive agents, anti-inflammatory drugs, and anticoagulants for example. Other interactions such as cytochrome inhibition have been identified, resulting in increased drug exposure.
Conclusion: Our study highlights the importance that ADRs resulting from DDIs have in Public Health. Healthcare professionals face an important challenge with the increasing prevalence of polypharmacy, particularly in aging populations with multiple comorbidities which accentuates the importance of understanding and managing these interactions and avoiding placing an additional burden on healthcare systems and resources.
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11
Acute Autoimmune Hepatitis Following COVID-19 mRNA Vaccination: A Population-Based Study Using Electronic Health Records in Singapore

Amelia Jing Jing Ng[1], Desmond Chun Hwee Teo[1], Sreemanee Raaj Dorajoo[1], Aaron Jun Yi Yap[1], Wan Cheng Chow[2], Nicholas Kai Ming Ng[1], Sally Bee Leng Soh[1]

[1]Health Sciences Authority, Singapore, Singapore. [2]Singapore General Hospital, Singapore, Singapore

Introduction: Reports of coronavirus disease 2019 (COVID-19) vaccine-induced autoimmune hepatitis (AIH) have been largely limited to case reports and case series. To date, only one population-based study using spontaneous reports related to AIH in the Vaccines Adverse Event Reporting System (VAERS) in the United States had examined the association between COVID-19 vaccination and AIH, which is limited by under-reporting.[1]
Aim/Objective: To investigate the association between COVID-19 mRNA vaccination and AIH.
Methods: We conducted a nationwide study using a nationally aggregated electronic health records database, which captures all visits to public healthcare institutions in Singapore. Patients of all ages with acute presentations of AIH (AAIH) between 1 January 2019 and 28 February 2023 were identified using a combination of diagnosis codes and laboratory tests. Cases for inclusion were confirmed by chart reviews. AAIH was defined as the presence of one or more hepatitis-related signs and symptoms reported up to 3 months prior to admission, deranged liver function tests, as well as biopsy results characteristic of AIH or response to steroid treatment for patients who did not undergo biopsy. We performed observed-over-expected (O/E) analyses and Self-Controlled Case Series (SCCS) to examine the potential association of COVID-19 mRNA vaccinations with AAIH in our local population.
Results: Seventy-six patients fulfilled our case definition of AAIH within the study period, with 6 patients having an estimated onset within 42 days of COVID-19 mRNA vaccination. All 6 patients were females above 40 years old. In the O/E analysis for this demographic group, point estimates of the rate ratios were approximately 3 times higher during the risk window than periods outside of the risk windows, although confidence intervals were wide [21-day risk window: Rate ratio (RR) 3.54 (95% confidence interval (CI) 0.26–322.64); 42-day risk window: RR 3.15 (95% CI 0.46–48.44)]. Similar results were observed at the population level, albeit at a lower magnitude [21-day risk window: RR 2.54 (95% CI 0.22–84.41); 42-day risk window: RR 2.23 (95% CI 0.38–19.90)]. In the SCCS analysis, the relative incidence of AAIH among females 40 years and above, and among all sex and age groups were 1.96 (95% CI 0.50–7.76) and 2.02 (95% CI 0.53–7.65) respectively in the 42 days following COVID-19 mRNA vaccination.
Conclusion: Our findings suggest that COVID-19 mRNA vaccination does not appear to be associated with increased risk of AAIH requiring admissions in the population, although larger studies are required to confirm these findings.
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Adverse Drug Reaction Monitoring in Psychiatric Patients at Tertiary Care Hospital

Prerana Sankhla[1], Dilip Rangi[1], Narendra Bheemraj Parihar[1], Jitendra Jeenger[2], Mahendra Singh Rathore[1]

[1]Geetanjali Institute of Pharmacy, Udaipur, India. [2]Geetanjali Medical College and Medical, Udaipur, India

Introduction: Psychotropic medications are abondened in number and their use is increasing gradually. These medication are able of causing several adverse drug reactions (ADR), some of which may be harmful. ADR's associated with psychotropic medicines can lead to resistance and at times termination of remedy. Psychotropic medicines used at normal doses, have been associated with ADR's. Unplanned reporting of suspected ADR's, particularly useful in identification of rare and late responses.
Aim/Objective: To determine and access the adverse drug reactions in psychiatric patients in tertiary care hospital.
Methods: A prospective observational study was conducted in a tertiary healthcare population of a psychiatric department at a Geetanjali hospital for the period of 6 months. We used the consecutive sampling technique in which 140 adult patients from 18 years to 65 years were observed. In this, time dependent study. ADR's were monitored by Naranjo causality and Hartwig's severity assessment scales in which WHO prescribed indicator were used. Data collected was analyzed with the help of the Statistical Analysis using SPSS V 25.0.
Results: Most of the ADR were observed in age group of 28-37 years (47.8%) 140 patients were screened for the ADR, from which 36 patients were found to be experiencing at least one ADR. The overall incidence of ADR's observed in outpatient to be 25.70%, in which 8 (22.22%) were female and 28 (77.8%) were male. According to

residential status of the patients ADR's observed were 25 (69.5%) in urban and 11 (30.5%) in rural population. Fatigue (36.10%) is the most common suspected ADR. Olanzapine 11(19.20%) was the frequent causing drug which leads to ADR. No ADR were observed during the study which turned to be lethal, life-threatening or needed any hospitalization emergency. Most of the suspected ADRs comes out to be 'probable' (55.56%) followed by 'possible' (22.22%), 'doubtful' (11.11%), 'definite' (11.11%). Hartwig Severity Assessment Scale was used for observing the severity of suspected ADR's in which most were 'mild' 32 (88.89%) followed by 'moderate' 4 (11.11%).

Conclusion: Study revealed that most of the ADRs reported during the study were mild and surely preventable type. Daily monitoring of ADRs in psychiatry OPD settings might help. Clinical Pharmacist plays an important role in minimizing the problems caused by ADR and thereby it may improve patient quality of life, reduce treatment cost, and escalate compliance with the treatment and they provide a patient counseling for at least 20 minutes and medical adherence data properly.

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Real-World Data Obtained from Active Surveillance of Adverse Events Following Vaccination with COVID-19 Vaccines Using the Mobile App SafeVac 2.0

Larissa Kopp, Dirk Mentzer

Paul-Ehrlich-Institut, Langen, Germany

Introduction: Vaccinations are essential for prevention of severe disease due to infections and the thereof potentially resulting health impact in the population. To guarantee the administration of safe vaccines, post-marketing safety surveillance is indispensable.

Aim/Objective: The objective of the study was the evaluation of the safety of COVID-19 vaccines in vaccinated people 12 years of age and older in Germany, who received at least one COVID-19 vaccine.

Methods: SafeVac 2.0 was a prospective non-interventional population-based, active surveillance study performed in Germany using a mobile app. Participants could register via smartphone within 48 hours after the administration of the first or second dose of a COVID-19 vaccination. Information regarding participants and vaccinations with the option to register up to three doses of a COVID-19 vaccine and the tolerability of the vaccination was collected. At pre-specified time points, participants were asked if adverse events following immunization (AEFI) occurred or not.

Results: 739,517 vaccinees participated in the study. Participants were analyzed regarding sex, age and age groups, height, weight and BMI and BMI group. Gender distribution of participants was comparable with 50.67 % of patients being female, 49.15 % being male and 0.18% being divers. Median age was 41 years (range 12 to 120 years, mean 43.04 ± 15.0 years). Women were overall slightly smaller and had a lower weight and BMI compared to men.

1,405,286 vaccination doses were reported with most participants receiving mRNA vaccines (82.26 %), followed by vector-based vaccines (17.31 %). Most registered vaccinations related to the first dose administered (52.12 %) or the second dose (33.82 %), though there were still 14.05 % registered booster doses. The course of registered vaccinations and doses is comparable to the vaccinations and doses administered during the vaccination campaign in Germany. Regarding tolerability, the largest amount of reported Adverse events following immunization (AEFI, 79.15 %) were chosen from pre-specified solicited events, which are known and labeled in the product information of these vaccines. Around 1.28 % of reported AEFIs were classified as serious.

Conclusion: Analysis of the data showed that the study population regarding descriptive data is comparable to the general population vaccinated in Germany thereby representing a real-world dataset in pharmacovigilance, which was collected prospectively to investigate tolerability and safety of COVID-19 vaccines. More specific analysis of the received data can be performed to specifically evaluate the overall safety profile of COVID-19 vaccines and to determine the importance of real-world data in pharmacovigilance based on a dataset with a very high number of participants.

References

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Pitfalls in the Management of Pharmacokinetic Drug-Drug Interactions: a Focus on Anticalcineurins and Azole Antifungals

Francoise Livio[1], David Haefliger[1], Catia Marzolini[1,2,3]

[1]Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. [2]University Hospital Basel, Basel, Switzerland. [3]University of Liverpool, Liverpool, United Kingdom

Introduction: A proportion of preventable adverse drug reactions are due to pharmacokinetic drug-drug interactions (DDIs), for instance when one drug inhibits the metabolism of another, thereby increasing the exposure of the impacted drug and the related risk of toxicity. Yet, adequate management of DDIs may be challenging, as dosing recommendations are generally not provided in the SmPC unless specific DDIs studies have been carried out. Online tools are useful, but do not cover all drugs or do not systematically provide dosing recommendation to overcome a given DDI.

Aim/Objective: To highlight points to consider to best manage DDIs and ensure safe prescribing.

Methods: Two cases of DDIs between anticalcineurins and azoles are presented. Tacrolimus and cyclosporine have a narrow therapeutic index and are metabolized by CYP3A4/5 and CYP3A4, respectively. Azoles are CYP3A inhibitors. Based on these cases, some pitfalls relating to DDIs assessment are reviewed.

Results: 41-year-old male with lung transplantation treated with tacrolimus 7 mg po bid resulting in stable tacrolimus trough plasma concentrations (Cmin) within the target range (10-12ng/mL). Two days after introducing isavuconazole, tacrolimus Cmin was > 30ng/mL.

Isavuconazole is a moderate CYP3A4/5 inhibitor (AUC of sensitive substrates increased by ≥2-<5-fold).[1,2] In one study, coadministration with isavuconazole increased tacrolimus AUC by 2.2-fold, and

cyclosporine AUC by only 1.3-fold.[3]Although both anticalcineurins share the same metabolic pathway, they are not equally sensitive to the inhibitory effect of isavuconazole. Thus, DDIs data cannot be automatically inferred from one drug to another.

12-year-old male with allo-SCT treated with cyclosporine 60 mg iv bid. Cyclosporine dose was reduced to 2x48 mg iv bid when posaconazole was introduced. Cyclosporine Cmin remained within the target range (180-250ng/mL) on the subsequent days. Cyclosporine was later switched to oral route and dose was increased to 96 mg bid to account for low oral bioavailability. Two days later, Cmin was 630ng/mL.

Posaconazole is a strong CYP3A4 inhibitor (AUC of sensitive substrate increased by ≥5-fold).[2] DDI-based dosage adjustment may differ according to the route of administration, particularly for drugs with high intestinal/hepatic metabolism, such as cyclosporine or tacrolimus (lower dose if po).

Conclusion: Managing DDIs requires expertise. In difficult cases, pharmacologists/pharmacists can provide valuable assistance. TDM is useful to check the appropriateness of dosage adjustments. PBPK modeling will enable to better characterize DDIs.

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Challenges Faced By Medicines And Therapeutic Committees In Regional Referral And District General Hospitals In Eastern And North Eastern Uganda

Douglas Mwesigwa

National Drug Authority of Uganda, Kampala, Uganda

Introduction: The Ministry of Health Uganda (MoH), with support from National Drug Authority (NDA) built capacity amongst Medicines and Therapeutics Committee members at health facilities to enhance detecting, assessing, understanding, managing and reporting of adverse drug reactions (ADRs). (Ministry of Health, 2018) Despite these efforts, reporting of ADRs to NDA has remained suboptimal.

Aim/Objective: To establish the functionality and challenges faced by the Medicine and Therapeutic Committees and their subcommittees in regional referral and district general hospitals of Eastern and North Eastern Uganda in ensuring rational drug use.

Methods: A cross sectional survey employing mixed methods; qualitative and quantitative methods of data collection on all the variables under study. Aspects such as; MTCs that have regular meetings at least once a quarter, MTCs that had well constituted pharmacovigilance (PV), antimicrobial stewardship and supply chain subcommittees, if the PV subcommittee meets to discuss adverse drug reactions regularly, if the PV subcommittee has had refresher training in the last 6 months. Members of MTC including the chairperson, secretary and the secretaries of subcommittees and other members of the committee were also interviewed on challenges faced by the MTCs in form of key informants' interviews.

Results: 11 health facilities, 2 regional referral hospitals, 9 general hospitals i.e. Mbale and Moroto Regional Referral Hospitals, Kotido, Amudat, Kaabong, Abim, Busolwe, Bududa, Pallisa, Kapchorwa, Tororo and Masafu General Hospitals were assessed between 17th to 28th July 2023. Results presented descriptively; Health Facility MTCs that have regular meetings were (n = 10, 91%), those with subcommittees formed (n = 9, 82%), those with Pharmacovigilance subcommittee that meets regularly to discuss adverse events reports (n = 4, 36.6%), those with regular training and refreshers in Pharmacovigilance within the last 6 months (n = 8, 73%).

Conclusion: Despite majority of the health facilities having in place MTCs that sit regularly, challenges noted were; a gap in awareness of the MoH MTC manual, poor attitude of health workers towards reporting ADR, insufficient facility budgets usually missing allocating votes to the MTCs.

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Economic Burden of Hospital Admission Due to an Adverse Drug Reaction in France: the IATROSTAT ECO Study

Marie-Laure Laroche[1], Marie-Blanche VALNET-RABIER[2], Noémie Tarbouriech[3], Virginie Nerich[3,4]

[1]Centre Régional de Pharmacovigilance et d'information sur le médicament, CHU Limoges, LIMOGES, France. [2]Centre Régional de Pharmacovigilance et d'information sur le médicament, CHU Besançon, Besançon, France. [3]Pole Pharmacie, CHU Besançon, Besançon, France. [4]Université de Franche-Comté, CHU Besançon, INSERM, EFS-BFC, UMR 1098, Pôle Pharmacie, Besançon, France

Introduction: The IATROSTAT study, the last French study about hospital admissions for adverse drug reactions (ADR-HA), estimated its incidence in 2018 at 8.5% (95% CI: 7.6–9.4), i.e. 212 500 estimated annual hospitalisations (1). Few studies are available on the impact of ADR-AH on healthcare expenditure.

Aim/Objective: To estimate the economic burden of ADR-HA in France.

Methods: We conducted a partial economic evaluation from the French public health insurance perspective. This cost description included only direct medical costs, collected retrospectively from the French Hospital Discharge Database (*Programme de Médicalisation des Systèmes d'Information*, PMSI), and related to hospital stays (hospital stays, daily supplements and medicines products and medical devices on top of Healthcare Resource Group (HRG)-based tariffs), and specific external consultations and other clinical and technical medical procedures. The economic burden was estimated by calculating the total cost per patient with ADR-HA *via* summation of the cost of hospital stays, daily supplements, medicines products and medical devices on top of HRG-based tariffs, and specific external consultations and other clinical and technical medical procedures, over 3 months from the first day of ADR-HA. The robustness of the results was assessed through one deterministic 1-way sensitivity analysis focused on cost drivers applying tariffs 2023 instead of tariffs 2018.

Results: Of the 309 patients included in the IATROSTAT study, 196 patients were included in the IATROSTAT-ECO study (65.5% of hospital wards agreed to participate int the economic part of the study). Patients' characteristics between the two studies were similar, except for a greater number of older patients and patients with acute renal failure in the IATROSTAT-ECO study. According to tariffs 2018 (vs 2023), the mean total cost per patient with ADR-HA was estimated at €5,208 ± 3,719 (€5,974 ± 4,232) with a range from €514–€23,355 (€618–€27,380). The total cost for 196 patients included in the IATROSTAT-ECO study was estimated at €1,020,549

(€1,170,960). It could be estimated at a minimum of €1 billion at the French national scale.

Conclusion: In addition to the increase in expensive drugs, the aging population and the polypharmacy, the economic impact of serious adverse events leading to hospitalisation weighs heavily on healthcare spending.

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Promoting Curricular Inclusion of Pharmacovigilance Awareness Among Medical Students Through A Research Skill Training Module

Maxine Gossell-Williams

Section of Pharmacology and Pharmacy, Faculty of Medical Sciences, The University of the West Indies, Kingston 7, Jamaica

Introduction: Pharmacovigilance as a part of medical curricular inclusion is poor [1] and innovative methodologies to fill this gap are needed. The Pharmacovigilance Scholar Research Programme was introduced in 2019 as a Special Study Module of the curriculum of medical students [2].

Aim/Objective: To describe the use of research skills training to support pharmacovigilance awareness among medical students.

Methods: Between the years 2019 and 2023, medical students of the Faculty of Medical Sciences, at The University of the West Indies were invited to participate in a module from May to June to introduce pharmacovigilance and its importance to clinical practice. Each student was guided through a research project focused on objectives specific to the World Health Organization definition of pharmacovigilance, using published patient case reports of adverse drug reactions. Students completed a poster and a three-minute pre-recoded video of the poster. The module ended with presentation of the posters at a mini-symposium open to the public. A Facebook (FB) page was created in June 2020 for optional sharing of poster to facilitate social median interaction through likes (L), comments(C) and shares(S). Students were also encouraged to consider sharing their work through other scholarly modalities. Data analysis involved collecting comments from students on their experience with the module; FB engagement rate as of March 17, 2024 (L+2C+3S)/(sum of the engagement weight x number of followers of FB page)[3] was calculated for each poster uploaded and values $\geq$ 0.01 considered as good FB engagement rate [4].

Results: Participant numbers increased from 10 in 2019 to 28 students in 2023; Comments from students suggest the objectives of the module were achieved and participants were overall satisfied with the experience. Of the 74 posters uploaded on FB, the engagement rates ranged from 0.002 to 0.042; 17 (23%) of the posters showed good engagement rates and the top three popular posters were tocilizumab/demyelination (0.042) escitalopram/alopecia(0.028)and furosemide/drug rash with eosinophilia and systemic symptoms syndrome (0.023). Publications from the module include two full papers, one letter to editor and two conference abstracts.

Conclusion: This innovative learning methodology provided an engaging model to promote pharmacovigilance awareness among medical students. The opportunity to conduct research and share by multiple formats were additional benefits to students.

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Fluoroquinolone and Risk of Nightmares: A Disproportionality Analysis

Christian Tsobo Tsobo[1], Mohammad A Omrani[2], Chalabianloo Niaz[2], FLORY TSOBO MUANDA[2]

[1]Unit of Clinical Pharmacology, Kinshasa, Congo, the Democratic Republic of the. [2]Western University, London, Canada

Introduction: Despite some case reports linking fluoroquinolones to nightmares,[1] no real-world study has examined this association using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database. We conducted a disproportionality analysis to quantify the risk of nightmares associated with the use of fluoroquinolones.

Aim/Objective: To determine whether fluoroquinolones are associated with a higher risk of nightmares compared to other medications.

Methods: We analyzed adverse drug events (ADEs) reported to FAERS databases from 2004Q1 to 2023Q3 using Openvigil 2.1-Medical Dictionary for Regulatory Activities (MedDRA)-v24. The outcome of interest was the MedDRA preferred term 'nightmare.' The study drugs included ciprofloxacin, levofloxacin, moxifloxacin, and other drugs. We used reporting odds ratios (ROR) to compare the proportion of nightmare reports for fluoroquinolones to those for other drugs to detect signals. We also repeated the primary analysis with three active comparator groups that share similar indications with fluoroquinolones, including azithromycin, nitrofurantoin, sulfamethoxazole, and trimethoprim. All analyses were restricted to ADEs considered the primary suspects in the database.

Results: Our results showed that levofloxacin (215 cases of 25,480 [0.84%] vs. 20,460 cases of 11,711,653 [0.17%]; ROR, 4.86 [95% CI, 4.25 to 5.57]), ciprofloxacin (207 cases of 25,471 [0.81%] vs. 20,468 cases of 11,711,662 [0.17%]; RR, 4.68 [95% CI, 4.08 to 5.37]), and moxifloxacin (49 cases of 13,145 [0.37%] vs. 20,626 cases of 117,723,988 [0.18%]; RR, 2.12 [95% CI, 1.60 to-2.81]) had a higher proportion of reports of nightmares compared to other medications. In contrast, no signal was observed with azithromycin, nitrofurantoin, sulfamethoxazole and trimethoprim.

Conclusion: Fluoroquinolones may be associated with a higher risk of nightmares. These findings have important implications for patients and

healthcare providers. Further pharmacoepidemiologic studies are needed to confirm this association and inform appropriate prescribing practices.

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Pharmacovigilance Assessors' Experiences Interacting with Narrative Fields in Spontaneous Reports: An Exploratory Interview Study

Joana Félix China, Alem Zekarias, Eva-Lisa Meldau, Johan Ellenius

Uppsala Monitoring Centre, Uppsala, Sweden

Introduction: In pharmacovigilance (PV), structured data elements for adverse event reporting play an important role but may not capture all relevant details, such as the patient's full clinical course or other contextual information. The narrative fields (*Narrative Case Summary* and *Relevant medical history*, according to ICH E2B R3[1]), can provide a more detailed account of the adverse event, offering important insights not reported in structured data fields[2].

Aim/Objective: To explore how and why pharmacovigilance assessors interact with the case narrative fields in spontaneous reports to better understand their challenges and needs, paving the way for future developments and support.

Methods: We conducted semi-structured interviews with five PV specialists, three pharmacists and two medical doctors, who had an average of 14 years of hands-on experience working with signal detection and assessment. The participants were all purposively selected from four national regulatory pharmacovigilance centers, covering four geographically and societally different countries. Interviews were recorded, transcribed, and analyzed using thematic content analysis.

Results: We identified four main themes and their respective subthemes (Table 1): narratives' content and value; processes utilizing the narratives; challenges assessors face and their needs when interacting with the narratives.

All interviewees viewed the narrative as a source of useful clinical information used in multiple steps of signal management. The narrative provides a "*full clinical picture*", a chronological storyline that is difficult to obtain from the structured fields. However, assessors often face challenges with uninformative, repetitive, and incomplete narratives despite established guidelines and recommendations on how narratives could be written. This quality issue requires assessors to complement the narrative's information either using discharge letters or through multiple follow-ups with the initial reporter to better understand the full clinical picture.

Furthermore, assessors struggle with the identification of informative narratives and with the extraction of the relevant clinical information. Assessors' needs are determined by the main challenges they face when interacting with the narratives or with ways to improve their current manual processes.

Table 1. Themes and sub-themes identified during the interviews

Themes	Sub-themes
Content and Value	• The fundamental importance of the narratives • Variability in completeness of information • Narratives as a source of clinical information
Processes	• Case by case analysis • Coding and Code validation • Prioritization/Triage • Case assessment • Interaction with reporters and completion of narratives
Challenges	• Time-consuming narratives • Extracting data from the narratives • Identifying informative narratives • Lack of understanding by reporters on how to write a complete narrative.
Needs	• Automated guidance when writing the narratives. • Automated triage of reports • Automated identification of index cases • Automated identification and extraction of entities from the narratives • Automated rewrite and restructuring of the narratives. • Automated causality assessment

Conclusion: Despite challenges in the interaction with case narratives, PV-assessors consider them the hallmark of suspected adverse event reports. Our study stresses the need for a clear implementation of what should be reported in the narratives. The study's insights highlight the importance of considering assessors' experiences with the narratives in the development of innovative tools.

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Association Between the NAT2 Gene and Pyrazinamide-Induced Liver Injury in Peruvian Patients with Tuberculosis

Teodoro Oscanoa[1,2,3], Oscar Acosta[4,5], María L. Guevara-Fujita[4], Ricardo Fujita[4], Saul Moscol[3], Roman Romero-Ortuno[6,7]

[1]Universidad de San Martín de Porres. Facultad de Medicina Humana, Centro de Investigación de Seguridad de Medicamentos, Lima, Peru. [2]Universidad Nacional Mayor de San Marcos. Facultad de Medicina, Lima, Peru. [3]Hospital Nacional Guillermo Almenara, EsSalud, Lima, Peru. [4]Universidad de San Martín de Porres. Facultad de Medicina Humana, Centro de Investigación de Genética y Biología Molecular, Lima, Peru. [5]Universidad Nacional Mayor de San Marcos, Facultad de Farmacia y Bioquímica, Lima, Peru. [6]Discipline of Medical Gerontology, Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland. [7]Global Brain Health Institute, Trinity College, Dublin, Ireland

Introduction: The association between the N-acetyltransferase 2 (NAT2) gene and hepatotoxicity, specifically drug-induced liver injury (DILI) caused by antituberculous drugs, is well-established [1]. However, previous studies have predominantly focused on the concurrent administration of antituberculosis drugs such as isoniazid, rifampicin, and pyrazinamide, or isoniazid alone in prophylactic therapy. There is a need for investigations into the relationship

between polymorphisms of the NAT2 gene and pyrazinamide-induced liver injury (PILI).
Aim/Objective: This study aimed to examine the association between six polymorphisms of the NAT2 gene and PILI in Peruvian patients.
Methods: This observational study was conducted at the Almenara ESSALUD Hospital in Lima, Peru. The diagnosis of DILI was based on the criteria set by the DILI-Expert Working Group, and causality analysis was performed using the Roussel Uclaf Causality Assessment Method (RUCAM). Specific association with PILI was determined through processes such as rechallenge, suspension, and recovery. Six polymorphisms of the NAT2 gene were studied: rs1799929 (c.481C>T), rs1799930 (c.590G>A), rs1799931 (c.857G>A), rs1041983 (c.282C>T), rs1801280 (c.341T>C), and rs1208 (c.802G>A). Associations were considered significant when $p < 0.05$..
Results: Forty patients with tuberculosis (mean age: 42.9 ± 18.1 years; 51.7% female) were included in the study. Ten patients experienced PILI (cases), while 30 were non-DILI (controls). For the rs1041983 polymorphism (c.282C>T), the Odds ratio was 4.57 (95% CI: 0.83- 25.21) when analyzed as CC vs CT+TT, and 3.361 (95% CI: 1.18- 9.61) when analyzed as C vs T, indicating an association and risk of PILI with the T allele. No significant association was found with the other NAT2 polymorphisms studied.
Conclusion: Preliminarily, the evaluation of six NAT2 gene polymorphisms indicates an association only between rs1041983 (c.282C>T) and PILI in Peruvian patients with tuberculosis. Further studies with a larger number of cases are necessary to validate these findings.
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Medication-Related Falls in Older Adults: A Bibliometric Review of Global Research

Haona Li[1,2], Zhihua Yue[3], Peiming Yu[4], Junkai Shen[4]

[1]School of Medicine, Henan University, Kaifeng, China. [2]Quality Use of Medicines and Pharmacy Research Centre, Clinical and Health Sciences, University of South Australia, adelaide, Australia. [3]Chinese Pharmacopoeia Commission, Beijing, China. [4]School of Pharmacy, Henan University, Kaifeng, China

Introduction: Falls and fall-related injuries have long been a major public health problem, and are expected to be more pressing with the aging of population. [1, 2] Medications, as an important risk factor for falls and fall-related injuries in older adults, have been intensively and extensively studied. [3, 4]
Aim/Objective: From the developments of the literature, we derived the following research questions: (1) What is the structure of global research in medication-related falls? (2) How did it develop over time? and (3) What are the consequences for future research on medication-related falls? This study uses quantitative methods to classify bibliometric data and build up representative summaries and summarized the research status, development stages, and potential trends of the field.
Methods: CiteSpace V (version 6.1.R2) was used in this Bibliometric analysis to provide insights into current research status and emerging trends in this field.
Results: This bibliometric review presents detailed information on the bibliometric features of the research field. There were 199 publications retrieved from WoSCC from 1985 to 2022. The collaborative network consists of 881 authors from 424 institutions, 36 countries, forming 2393 cooperative relationships of authors, 760 cooperative relationships of institutions, 79 cooperative relationships of countries. The 199 publications in total were published in 104 peer-reviewed journals, 101 of which published on top 15 journals, accounting 50.75% of the total. There were 280 keywords forming 895 co-occurrence relationships. Most researches were conducted in developed countries, and left developing countries falling behind. There was a serious lack of bridging institutions in the collaborative network and call for key research institutes to take the leading and bridging role in the research.
Conclusion: Countries, institutions, or authors, with high frequencies, high centralities or high strengths of bursts, formed the basic and core parts of the comprehensive collaborative network. Keywords with high frequencies, high centralities, or high strengths of bursts, provided comprehensive information for understanding the evolution of hot topics and emerging trends in the research field.
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Changing the Course of the Opioid Epidemic One Risk Communication at a Time

Xi Jin (Susie) Wang[1,2], Myriam Salem[1]

[1]Health Canada, Ottawa, Canada. [2]McGill University, Montreal, Canada

Introduction: While prescription opioids are an important option for managing pain, they may lead to opioid-related harms, such as overdose and death.[1] The Marketed Health Products Directorate (MHPD) at Health Canada (HC) regularly reviews safety signals and in turn releases risk communications (RCs) for marketed opioids. Since the effectiveness of this strategy is yet to be characterized, here, we looked at the trends of opioid prescriptions and opioid-related adverse events in Canada, in relation to HC-released risk communications for the period of January 1, 2018 to December 31, 2022.
Aim/Objective: To examine the 5-year trends of opioid related prescriptions in Canada coupled with an analysis of HC-issued risk communications (RCs) for the period of January 1, 2018 to December 31, 2022.
Methods: Five types of RCs released for List B opioids were retrieved from the Government of Canada websites: Health Product InfoWatch, Dear Healthcare Professional Letter, HC-endorsed important safety information, Public Advisory, and Summary Safety Review. Drug purchasing and dispensing data (Canadian Drugstore and Hospital and CompuScript) were retrieved from the IQVIA database for Health Canada. Finally, the Canada Vigilance Database was consulted for serious reports, under narrow Standardised

MedDRA Queries (SMQs) for "Drug abuse and dependence" and "Drug withdrawal" (MedDRA version 26.0). Figures were generated using RStudio.

Results: HC released a total of 30 RCs for List B prescription opioids during the 5-year study period, with a notable peak of 13 RCs in 2020. In contrast, the number of drugstore- and hospital-purchased opioids markedly declined from 2018 to 2021 (1.96 to 1.71 billion extended units; 1 extended unit = 1 mL or 1 tablet). Interestingly, however, a slight increase in purchasing activity was noted in 2021 with a continuous steady increase into 2022. Adverse event reports (AERs) showed no clear trend and appeared to fluctuate throughout the study period, with the lowest number of reports in 2020 (n = 380) and the highest in 2021 (n = 1167).

Conclusion: The current data suggest an impact between the release of opioid-related communications and decline in drugstore- and hospital-purchased opioids. More datapoints are required to conclude on trends with respect to the association between issuance of the RCs and AERs. In conclusion, the study highlights the importance of continued public awareness of opioid-related harms, which can be further evaluated through the assessment of effectiveness of risk minimization tools in place for prescription opioids.

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Effect of the *CYP4F2* Gene on Warfarin Dose in Anticoagulated Peruvian Patients

Teodoro Oscanoa[1,2,3], María L. Guevara-Fujita[4], Ricardo M. Fujita[4], Oscar Acosta[4,5], Maria Y. Muñoz-Paredes[6], Alfonso Carvajal[7]

[1]Universidad Nacional Mayor de San Marcos. Facultad de Medicina, Lima, Peru. [2]Hospital Nacional Guillermo Almenara, EsSalud, Lima, Peru. [3]Universidad de San Martín de Porres. Facultad de Medicina Humana, Centro de Investigación de Seguridad de Medicamentos., Lima, Peru. [4]Universidad de San Martín de Porres. Facultad de Medicina Humana, Centro de Investigación de Genética y Biología Molecular, Lima, Peru. [5]Universidad Nacional Mayor de San Marcos, Facultad de Farmacia y Bioquímica, Lima, Peru. [6]Hospital de Emergencia Grau, Servicio de Hematologia, ESSALUD, Lima, Peru. [7]Universidad de Valladolid, Valladolid, Spain

Introduction: The CYP4F2 gene encodes the enzyme CYP4F2 (cytochrome P450 4F2), which is responsible for the primary metabolization of vitamin K in the liver. It is known that one of the pharmacogenes that influence the dose of Warfarin is the CYP4F2, although the degree differs depending on the type of gene and the populations studied [1].

Aim/Objective: To study the effect of the CYP4F2 gene on the dose of warfarin in Peruvian patients.

Methods: A descriptive and ambispective observational study was carried out with patients seen in the Grau ESSALUD Hospital, Hematology Service, Lima, Peru, selected by non-probabilistic convenience sampling. The inclusion criteria were patients anticoagulated for more than three months and with stable doses of warfarin (same dose for at least three outpatient visits and with an INR in therapeutic ranges of 2.0-3.0). Analysis of the CYP4F2 gene, rs2108622 variant (C>T) , was performed by isolation DNA from peripheral blood and PCR-RFLP technique with PvuII enzyme.

Results: Seventy patients with a mean age of 69.6 $^{\pm}$ 13.4 years, male 38 (54.4%) and female 32 (45.7%) entered the study. The mean dose of warfarin was 31,6 + 15,2 mg/week. The genotypic frequencies of the rs2108622 variant in CYP4F2 gene were CC = 78%, CT = 19% and TT = 3%, no deviation from the Hardy-Weinberg equilibrium was found (p = 0.56). Mean ± SD warfarin doses by genotypes were CC = 30.3 ± 12.0; CT = 36.4 ± 25.6 and TT = 36.35 ± 1.8 mg/week, showing no significant differences (p = 0.397).

Conclusion: The rs2108622 polymorphism in CYP4F2 gene of the peruvians patients analyzed, do not have a significant effect on warfarin dose. More studies with a larger number of patients are necessary.

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Signal Detection of Drugs Associated with Obstructive and Central Sleep Apnoea

Clément Jambon-Barbara[1,2], Bruno Revol[1,2], Alex Hlavaty[1,2], Marie Joyeux-Faure[2], Jean-Christian Borel[2], Jean-Luc Cracowski[1,2], Jean-Louis Pepin[2,3], Charles Khouri[1,2,4]

[1]Grenoble Alpes University Hospital, Pharmacovigilance Unit, Grenoble, France. [2]Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, Grenoble, France. [3]Grenoble Alpes University Hospital, EFCR Laboratory, Grenoble, France. [4]Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, Grenoble, France

Introduction: Sleep apnoea (SA) is a global health problem affecting approximately 1 billion people worldwide. Several drugs have been suspected of causing or aggravating severity of SA through diverse pharmacological actions impacting some SA pathophysiological mechanisms, such as opioids, benzodiazepines, baclofen or testosterone (1,2). Given the wide prevalence of SA, its massive individual and societal impact, the demonstration of even a small increase in the risk of developing or worsening SA with the use of certain medications is of considerable interest.

Aim/Objective: We sought to discover new safety signals of drug-induced SA by investigating all drugs available and eligible to reimbursement in France between 2006 and 2018 using series of sequence symmetry analyses (SSA). To increase the robustness of our findings, the second step was to confirm and complement signals by performing disproportionality analyses in the World Health Organization (WHO) pharmacovigilance database.

Methods: We first conducted series of SSA (3-7) in a cohort composed from all patients who received a first SA diagnosis or treatment between 2006 and 2018 in the Echantillon Généraliste des Bénéficaires (EGB), a random sample of the French healthcare database. We used two primary outcomes to estimate the sequence ratio (SR) for all drug classes available in France: a sensitive one (diagnosis or treatment of SA) and a specific one (Positive Airway Pressure (PAP) therapy). We then performed disproportionality analyses using the "Bayesian neural network method" on all cases of sleep apnoea (MedDRA high level term) reported up to November 2023 in the WHO pharmacovigilance database.

Results: Among the 728,167 EGB individuals, 46,193 had an incident diagnosis or treatment for SA and 17,080 had started an incident treatment by PAP therapy. Fiftyeight drug classes had a significant SR, with 7 considered highly plausible: opium alkaloids and derivatives, benzodiazepine derivatives, other centrally acting agents, other anxiolytics, carbamic acid esters, quinine and derivatives and antivertigo preparations; with consistent signals found for the first 3 drug classes in the disproportionality analysis.

Conclusion: In this signal detection study, we found that 3 drug classes are highly plausibly associated with the onset or aggravation of sleep apnoea: opium alkaloids and derivatives (codeine, pholcodine, dextromethorphane), benzodiazepine derivatives

(lormetazepam, loprazolam, but not Z-drugs), and other centrally acting agents (thiocolchicoside, tetrazepam). Moreover, association with antivertigo preparations such as betahistine was unexpected and may be considered as a new safety signal that needs to be further explored.

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Drug Induced Enterocolitis Syndrome : A New Clinical Entity

Gwenaëlle VEYRAC[1], Ana Dagorn[1], Anne-Lise Ruellan[1], Caroline Joyau[1], Claire Bernier[2], Luc Colas[3]

[1]Clinical Pharmacology Department, CHU Nantes, Nantes, France. [2]Dermatology Department, CHU Nantes, Nantes, France. [3]Allergology Department, CHU Nantes, Nantes, France

Introduction: Drug-induced enterocolitis syndrome (DIES) is a rare allergic syndrome charactized and hilghlighted in recent years, with a semi-immediate (1 to 6 hours) digestive symptomatology that can lead to dehydration and even hypovolaemic shock. Very specific criteria which are derived from those of the older syndrome of enterocolitis induced by dietary proteins allowed to make a diagnosis.
Aim/Objective: Following the notification of 3 cases of DIES to the Nantes Regional Pharmacovigilance Center, the aim of this study was to retrospectively analyse cases of DIES in order to identify a clinico-biological profile and the suspected drugs.
Methods: We identified cases of DEIS from the literature, the French national (FPVD) and international pharmacovigilance database (IPD). The data included information on the patient's profile in terms of age, sex, usual or occasional drug treatment, and the drug suspected of being involved in the DEIS. The criteria for the diagnosis of DEIS, associated symptoms, time to onset of DEIS, skin test results, re-administration or discontinuation of treatments were listed.
Results: A total of 41 cases of DIES were identified from the FPVD, the literature and IPD. The cases were predominantly female (67%) and occurred more frequently in the paediatric population (67%). Digestive symptoms were the most common side effects reported, with vomiting consistently present (100%), followed by diarrhea (63%) and abdominal pain (60%). IgE sensitisation to the suspected drug was not detected in all the cases, although it was systematically reproducible after an oral provocation test. Biological data were reported in 9 cases. Neutrophilic polynucleosis (100%) and hyperleukocytosis (88%) were found. Methaemoglobinaemia was present in half of the cases. Finally, amoxicillin remains the drug most implicated in reported cases of DIES (75%).
Conclusion: In this study, a typical profile of this syndrome was drawn up by cross-referencing data obtained from various sources. This study also enabled us to show that amoxicillin is not the only molecule that can be correlated with the onset of DEIS, although it is the molecule predominantly represented. DIES remains an unrecognised entity with a predominance of paediatric and female patients.Its main digestive expression, the absence of detectable IgE sensitisation and the atypical time of onset (between 1 and 6 hours) mean that an allergic mechanism can usually be ruled out. The reproducibility of oral provocation test symptoms allows the diagnosis to be rectified. Following this series of cases, it remains essantial to inform health-care professionals and patients of the existence of this syndrome.

References

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Erythema Scarlatiniforme Desquamativum Recidivans with Amoxicillin: Study of the French Pharmacovigilance Database

Gwenaëlle VEYRAC[1], Amélie Mourtada[2], Hassan El Hanache[3], Sandrine Combret[4], Caroline Joyau[1], Anne-Lise Ruellan[1], Claire Bernier[2]

[1]Clinical Pharmacology Department, Nantes, France. [2]Dermatology Department, CHU Nantes, Nantes, France. [3]Allergology Department, CHU Nantes, Nantes, France. [4]Clinical Pharmacology Department, Dijon, France

Introduction: Erythema scarlatiniforme desquamativum recidivans (ESDR) (also known as Féréol-Besnier disease) is an uncommon skin condition characterized by recurrent desquamation, particularly of the palmoplantar surfaces in the localized form.
Aim/Objective: Following the notification of nine cases to the Nantes régional pharmacovigilance center, the aim of the study was to analyse all cases in the French pharmacovigilance database (FPVD).
Methods: ESDR does not exist in the MedDRA dictionary. A retrospective descriptive study using cases from the FPVD was carried out all suspected "skin exfoliation" (MedDRA Preferred Term PT) and "desquamation" (MedDRA Low Level Term LLT) reported with "amoxicillin" were extracted and analysed in the FPVD. We conducted a study of VigiBase international pharmacovigilance database.
Results: In total, 137 cases were collected in the FPVD, 48 cases were included after pharmacological analysis. The sex ratio (M/F) was 0.65 and the median age was 65 [1-95] years. There was only one suspect drug in 37 cases. The terms found in the notifications are desquamation of the skin, desquamated fingers, scarlatiniform rash, skin exfoliation. There were only 9 serious cases, the treatment was stopped in 39 cases and 39 times the patients were recovered.The disease was localized form in 40 cases, with 16 patients reporting a positive reintroduction of amoxicillin. Skin tests were negative on immediate and delayed reading in 15 cases. A VigiBase search using the term PT skin exfoliation found 427 cases with no CI (95% credibility interval) and with the LLT term "desquamation" 48 cases with a CI of 1.9.
Conclusion: The etiology of ESDR is still poorly understood. Among the factors, hyperergic reactions to drugs and to viral and bacterial infections (staphylococci and streptococci) have been suggested. Amoxicillin is not cited as the drug responsible, but the existence of positive reintroductions by patients themselves or by allergists without any notion of infection suggests its involvement in this reaction. The literature reports cases of ESDR involving amoxicillin [1]. ESDR is probably an under-diagnosed entity, particularly in its localised form. It is important to recognise this condition and avoid escalation in diagnosis and treatment.

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Masking Bias in Active Comparator Designs for Data Mining in Pharmacovigilance

ChenYang Bai[1], Antonios Douros[1,2,3], Christopher Gravel[1,2,4,5]

[1]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada. [2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada. [3]Charité - Universitätsmedizin Berlin, Berlin, Germany. [4]Department of Mathematics and Statistics, University of Ottawa, Ottawa, Canada. [5]Data Literacy Research Institute, Ottawa, Canada

Introduction: Masking is a reporting bias occurring when external factors trigger heightened reporting behaviours for a given drug. Masking can potentially muffle safety signals related to other drugs, resulting in false negatives [1]. While the impact of masking when screening across all reports of pharmacovigilance databases is often relatively limited, it is unclear how this bias affects estimates when using active comparator designs, where reference sets are restricted to drugs prescribed for common therapeutic purposes [2, 3].
Aim/Objective: To investigate the potential impact of masking when using active comparator designs in pharmacovigilance.
Methods: We used data from the United States Food and Drugs Administration Adverse Event Reporting System from 2010 to 2013. Rosiglitazone, an antidiabetic drug from the class of thiazolidinediones, which was recalled in 2010 due to concerns over risks of myocardial infarction (MI), was the potential masking candidate. We hypothesized that stimulated reporting related to these safety concerns could mask safety signals post-recall for pioglitazone, another thiazolidinedione. We computed proportional reporting ratios (PRR) with 95% confidence intervals (CIs) and Bayesian Confidence Propagation Neural Network (BCPNN) estimates with 95% credible intervals (CrI) for pioglitazone and MI under general screening versus active comparator, with and without rosiglitazone in the reference set, in the post-recall period. Relative differences in signal estimates were also assessed.
Results: In the presence of rosiglitazone, PRR (95% CI) estimates for pioglitazone and MI were 10.22 (9.23,11.25) under general screening versus 0.53 (0.48,0.58) with an active comparator. In the absence of rosiglitazone, the PRR (95% CI) was 16.08 (14.61,17.71) under general screening versus 18.52 (14.72,23.31) with an active comparator. In the presence of rosiglitazone, BCPNN estimates (95% CrI) were 0.99 (0.83,1.15) under general screening versus -1.41 (-1.57, -1.26) with an active comparator. In the absence of rosiglitazone, BCPNN estimates (95% CrI) were 1.14 (0.98,1.30) under general screening versus 1.02 (0.90, 1.13) with an active comparator. The relative difference in PRR estimates after rosiglitazone removal was 5.86 with general screening versus 17.99 with an active comparator. For BCPNN, the relative difference estimates were 0.15 with general screening versus 2.43 with an active comparator.
Conclusion: Masking can influence signal detection when using active comparator designs in settings where external events impact reporting rates of drugs in the reference set. The masking effect should be evaluated in related contexts for better public health decision-making in drug safety monitoring and triaging of resources for follow-up confirmatory studies.
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Association Between Drug Transporter Gene SLCO1B1 With Pyrazinamide-Induced Liver Injury in Peruvian Patients with Tuberculosis

Oscar Acosta[1,2], Teodoro Oscanoa[3,4,5], María L. Guevara-Fujita[1], Ricardo M. Fujita[1], Saul Moscol[5], Roman Romero-Ortuno[6,7]

[1]Universidad de San Martín de Porres. Facultad de Medicina Humana, Centro de Investigación de Genética y Biología Molecular, Lima, Peru. [2]Universidad Nacional Mayor de San Marcos. Facultad de Farmacia y Bioquímica., Lima, Peru. [3]Universidad de San Martín de Porres. Facultad de Medicina Humana, Centro de Investigación de Seguridad de Medicamentos., Lima, Peru. [4]Universidad Nacional Mayor de San Marcos, Facultad de Medicina., Lima, Peru. [5]Hospital Nacional Guillermo Almenara, EsSalud, Lima, Peru. [6]Discipline of Medical Gerontology, Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland. [7]Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland

Introduction: The drug induced liver injury (DILI) (hepatotoxicity), associated with antituberculosis drugs (isoniazid, rifampicin and pyrazinamide), is a severe adverse reaction during the treatment of tuberculosis (TB). According to pharmacogenetic studies, one of the multiple genes involved would be the drug transporter gene SLCO1B1, although the findings differ depending on the countries where the study is carried out [1, 2].
Aim/Objective: To study pyrazinamide-induced liver injury (PILI) associated with the SLCO1B1 gene in peruvian patients with tuberculosis.
Methods: An observational study was conducted in the Hospital Almenara ESSALUD in Lima, Peru. The criteria of the DILI-Expert Working Group were used for the diagnosis of DILI, and the RUCAM (Roussel Uclaf Causality Assessment Method) for causality analysis. Specific association with **PILI** was by the process rechallenge or suspension and recovery. DNA samples were obtained from peripheral blood for analysis using sequencing for detect variants in SLCO1B1 gene.
Results: The study included 39 patients with TB, nine PILI (cases) and 30 controls. The variants for SLCO1B1 gene: rs2306283(A>G), rs2291075 (C>T) and rs4149056 (T > C) were evaluated, being the most variables the genotypic and allelic frequencies of the rs2306283 in cases and controls: AA = 55.6%, AG = 33.3%, GG = 11.1%; A = 72.0%, G = 28.0% and AA = 36.7%, AG = 23.3%, GG = 40.0%; A = 58.0%, G = 42.0% respectively. In general, no significant association was found between the SLCO1B1 gene variants and PILI, however, there is a tendency for the reference A allele of the rs2306283 to be found more frequently in patients with PILI (p = 0.0746; OR = 2.779, IC 95%: 0.881-8.769).
Conclusion: In the Peruvian sample studied, no association was found between the SLCO1B1 gene and PILI, but with variability

between cases and control for the rs2306283(A > G). Studies with a larger number of cases are required.

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Cannabinoids and Adverse Convulsive Events: An Analysis of the French Pharmacovigilance and Addictovigilance Databases

Marion Labetoulle[1], Edeltraut Kröger[2,3,4], Arsène Zongo[2,3], Marie-Laure Laroche[1]

[1]Regional Center of Pharmacovigilance, CHU Limoges, LIMOGES, France. [2]Population Health and Optimal Health Practices Research Axis, CHU de Québec - University Laval Research Centre, Quebec City, Quebec, Canada. [3]Faculty of Pharmacy, University Laval, Quebec City, Quebec, Canada. [4]Centre d'excellence sur le vieillissement de Québec, Centre intégré universitaire de soins et services sociaux de la Capitale Nationale, Quebec City, Quebec, Canada

Introduction: The effects of cannabinoids are mainly associated with cannabidiol (CBD) and delta-9 tetrahydrocannabinol (THC). THC is considered to potentially have proconvulsivant effects as observed in certain subjects using cannabis sativa, and CBD to have anticonsulsivant effects. CBD, under the brand name Epidiolex®, is approved for use in patients with some specific types of epilepsy, but paradoxically adverse convulsive effect are frequently reported since its market authorization.

Aim/Objective: To study personal and product characteristics and usage circumstances that might explain the occurrence of seizures in subjects using cannabinoids according to the type of use: medical or recreational use/abuse.

Methods: We conducted a retrospective analysis of spontaneous reports of adverse drug effects issued by the French pharmacovigilance and addictovigilance systems and by manufacturers and recorded in the French Pharmacovigilance database, between 01/01/1985 and 21/07/2023. The request was based on the broad MedDRA SMQ term "convulsive" and the products included the terms THC, CBD, cannabis or natural cannabinoids. From the descriptive narrative of cases, we extracted the characteristics of individuals, the risk factors of seizures, including co-medication or illicit drugs associated with seizure. We stratified the results according to the type of use: medical or recreational use/abuse.

Results: Among 4296 notifications with the term cannabinoids, 130 (3%) reports of convulsive effects were extracted: 29 (23.3%) related to medical use (27 Epidiolex ®, 1 Marinol® and 2 combined THC/CBD preparations), 98 (75.4%) related to recreational use (cannabis sativa), and 3 cases related to accidental exposure to cannabis sativa in children. The median age was 29 years, 77.7% were men and 81.5% were serious cases including 8 deaths. Among the whole population, 82.3% of individuals had at least one risk factor seizures: 58.6% among those with medical use and 88.8% among those with recreational use. The main risk factors with medical use were concomitant epileptogenic drugs (41.4%), inefficacy (17.2%), and fatigue (13.8%). The main risk factors among those with recreational use were concomitant epileptogenic drugs (50.0%), consumption of illicit drugs (33.7%), and alcohol (32.7%).

Conclusion: In France, seizures are more frequently reported among recreational users of cannabis sativa, particularly in patients with other associated risk factors. The study also shows that more than half of patients using medical cannabis present additional risk factors for seizures. Educational information should be provided alongside the prescription of medical cannabis to prevent or minimize these adverse effects.

References

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Adverse Events Related to Etonogestrel Implant: An old but Still Current Issue?

João Paulo Fernandes[1], Márcia Silva[1], Margarida Sousa[2], Jani Bhikha[2], Paula Moreira[3], Isabel Silva[3]

[1]INFARMED I.P., Lisboa, Portugal. [2]ESTeSL, Lisboa, Portugal. [3]São João University Hospital Center, Porto, Portugal

Introduction: In December 2019, in Portugal, a Direct Healthcare Professional Communication (DHPC) was approved regarding the subcutaneous implant of etonogestrel 68 mg. The genesis of this communication was based on reported cases of neurovascular injury and migration of the implant from the insertion site within the arm, or, in rare cases, into the pulmonary artery, possibly associated with deep or incorrect implant insertion.

To minimize risks, the DHPC has introduced updates to the instructions for the insertion and removal of the implant [1].

Aim/Objective: The aim of our work is to conduct a descriptive analysis of the number of Individual Case Safety Reports (ICSRs) received by the Portuguese National Pharmacovigilance System (SNF) following the DHPC, related to adverse events associated with the insertion and removal of the etonogestrel implant.

Methods: Retrospective analysis of subcutaneous etonogestrel implant ICSRs reported to the Portuguese SNF, between 1 January 2020 and 31 October 2023. ICSRs were screened by 2 pharmacy students, and adverse events potentially associated with the insertion and removal of the etonogestrel implant have been flagged. All suspected migration ADR were clinically reviewed. Descriptive data analysis was performed.

Results: Our research retrieved 451 ICSRs related to the subcutaneous etonogestrel implant. In 32.2% (n = 145) of the total cases, it was reported that the implant was deeply located, with 12.4% (n = 56) specifically mentioning that it was located below the fascia. Around 8% (n = 35) of the cases had sufficient information to identify a case of migration to locations such as the axilla or the pulmonary artery. Ten migrations occurred in cases where the duration of use was between 3 and 5 years, and one migration occurred with usage exceeding 5 years. In cases where there was an incorrect duration of use exceeding 5 years, in 82.4% (n = 28) of them, the implant was found deeply located. Regarding the ICSRs of migration/implant deeply located, 57.8% (n = 104) mentioned complications associated with the implant removal.

Conclusion: Our results provide a general overview of adverse events associated with the etonogestrel implant. Despite inherent limitations in our study, it appears that this issue, although recognized, remains current. Further studies are needed to understand both the effectiveness of the additional risk minimization measures implemented and the potential need for new ones.

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Safety In Pregnancy Of Equine Antivenom In The Treatment Of Accidents With Poisonous Animals

Guillermo Alberto Keller[1,2], Guillermo Temprano[1], Lorena Romano[2], Claudio Bonel[1], Adolfo Rafael de Roodt[1], Jose Christian Dokmetjian[1]

[1]Instituto Nacional de Producción de Biológicos (ANLIS Malbrán), Ciudad Autónoma de Buenos Aires, Argentina. [2]Universidad de Buenos Aires, Facultad de Medicina, Centro de Vigilancia y Seguridad de Medicamentos, Ciudad Autónoma de Buenos Aires, Argentina

Introduction: Accidents linked to poisonous animals (snakes and arthropods) are pathologies of medical importance whose treatment continues to be based on the use of antivenoms (F(ab')2 equine sera). Despite the long-standing use of these therapeutic products, there is not enough data on the safety of their administration during pregnancy [1].
Aim/Objective: Provide safety information in pregnancy on the use of antivenoms for the treatment of accidents with poisonous animals, over the course of 5 years at the national level.
Methods: Illnesses linked to accidents with poisonous animals are mandatory reporting in our country. All cases are uploaded to an integrated national Argentine health information system, along with data linked to the characteristics of the event, health history (including whether the patient is pregnant), treatment performed, evolution, and outcome (discharge, hospitalization, death). The data were blinded, analyzed and compared with the case list of adverse reactions received from spontaneous reporting system using common data such as date, location, and type of accident. The frequency and relative risk linked to the events were analyzed using Statistica.
Results: A total of 40,948 reports of accidents linked to poisonous animals were identified. Of these, 140 cases were recorded in pregnant women (0.3%), corresponding to 115 cases of scorpionism, 16 araneisms (8 Loxosceles, 3 Latrodectus, 5 unspecified), 8 accidents with ophidians (all due to Bothrops) and 1 lonomiasis. Of these cases, 19 received administration of specific antivenom: 11 for scorpionism, 4 for Loxosceles, 4 for Bothrops. The patients who received the antivenom did not have comorbidities and had an average age of 31±11 (10-55) years. The subsequent evolution showed that all patients who received antivenoms were discharged, with complete resolution of the symptoms, without sequelae. Subsequent follow-up shows that none of these women experienced abortion, fetal malformations or other problems related to pregnancy.
Conclusion: Antivenoms show an adequate safety profile in pregnancy that, together with the potential benefit of their administration, must be considered in the event of an accident caused by poisonous animals in a pregnant patient.
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Preliminary Report Of Multicenter Study On Safety Evaluation Of Off-label Use Of Cannabis Products For Anxiety, Insomnia And Chronic Pain

Guillermo Alberto Keller[1], Jorge Alejandro Aimar[2], Daniel Chiacchiara[2], Florencia Nieto[2], Emilio García Habegger[2], Jaime Buchuck[2]

[1]Universidad de Buenos Aires, Facultad de Medicina, Centro de Vigilancia y Seguridad de Medicamentos, Ciudad Autónoma de Buenos Aires, Argentina. [2]Universidad de Buenos Aires, Facultad de Medicina, Centro de Canabis Medicina de la UBA (CECANNUBA), Ciudad Autónoma de Buenos Aires, Argentina

Introduction: Off-label use of cannabis products in Argentina has increased for insomnia, anxiety, and pain. No data about benefits, risks or adverse reactions has been properly described [1].
Aim/Objective: The objective of the work is to provide information on the safety and effectiveness of cannabis-derived products in insomnia, anxiety and chronic pain.
Methods: Through a multicenter, descriptive and retrospective design, records of 73 patients who used medicinal cannabis for insomnia, anxiety and/or chronic pain were analyzed. Population variables, history, reason for indication, therapy received (product, dose, time), controls, adverse reactions, tolerance, therapeutic response and modification of usual therapy were recorded. The improvement of symptoms that motivated the therapy and frequency and risk factors associated with adverse events were analyzed.
Results: 73 patients aged 45±19 (23-90) years (66% women), were treated for chronic pain (44%), anxiety (28%) or insomnia (18%). 62% had not previously used cannabis products. Chemotype 3 was more frequent in general (55%), and predominant in anxiety (100%) and insomnia (92%), while in pain chemotype 2 (56%) and chemotype 1 (44%) were used. The therapeutic response was satisfactory (93%), with no differences by indication (pain 97%, anxiety 93%, insomnia 85%) after 6±3 (1-12) months of follow-up, generating modification of base medication in 21%. Most of the patients discontinued treatment at the time of analysis (72%) due to improvement in symptoms. Adverse reactions occurred in 12% of patients (anxiety 4%, insomnia 8%, pain 22%), they were mostly mild (89%), (moderate only in 1 patient treated for pain, without severe cases or seriousness criteria). Regarding its signs and symptoms, the manifestation was headache (56% of RA), drowsiness (33%) or hypertension (11%), being predominant in patients treated in pain management (in anxiety and insomnia only isolated cases of drowsiness were registered). The analysis of factors associated with the risk of presenting adverse reactions showed statistical significance for QMT2 products (RR 6.00 [1.67-21.56]) and concentration by chromatography in the product of THC greater than 6 (5.58 RR 1.55 to 20.13), showing no statistical association when the reason for indication, age, gender, previous use of the product, and CBD concentration in the product were considered.
Conclusion: The use of cannabis-derived products in the treatment of insomnia, anxiety and chronic pain is associated with clear therapeutic benefits with few minor, clinically non-significant adverse reactions, ensuring an excellent risk/benefit profile.
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Drug-induced Liver Injury Assessment in VigiBase

Joana Félix China[1], Rita Baião[2,3], Monica Tarapues[1], Annette Rudolph[1]

[1]Uppsala Monitoring Centre, Uppsala, Sweden. [2]Local Health Unit Santa Maria University Hospital, Lisbon, Portugal. [3]Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine - University of Lisbon, Lisbon, Portugal

Introduction: Drug-induced liver injury (DILI) describes any liver injury occurring because of pharmacotherapy. Cases of liver injury qualify as DILI if certain clinical laboratory criteria are fulfilled[1]. Since no specific test confirms a DILI diagnosis, the Roussel Uclaf Causality Assessment Method (RUCAM)[2] is commonly used.

During a past routine disproportionality analysis, the combination venetoclax and hepatic failure was identified. In that case series we could not exclude confounding by indication or the causal role of concomitant drugs. Additionally, few reports fulfilled the DILI laboratory criteria and, due to missing information, the DILI-specific causality assessment method could not be applied.

Aim/Objective: To analyse reported DILI cases and assess whether the report quality found for venetoclax reflects DILI reports in VigiBase, the WHO global database of adverse event (AE) reports for medicines and vaccines.

Methods: An investigation using a random sample of 546 reports entered in VigiBase up to October 15th, 2023, containing the MedDRA PT "Drug-induced liver injury" and with populated ICH E2B (R3) fields was performed. The RUCAM algorithm was applied to cases fulfilling the CIOMS DILI case definition and with sufficient information to calculate the ratio of serum hepatic enzymes (R score)[1-3].

Results: Of 546 reports, only 272 (50%) met the DILI case definition. From the excluded reports, most lacked laboratory data (n = 211). Of the reports meeting the case definition, only 157 had sufficient information to calculate the R score and apply the RUCAM algorithm. This resulted in 64 reports with an overall assessment score indicating *possible DILI* and 13 reports indicating *probable DILI*. During the causality assessment, information on exclusion of alternative causes of liver injury as well as follow-up after dechallenge was often missing in the AE reports (n = 60).

Conclusion: In this study, the quality of data was found to be heterogeneous, which is a well-known characteristic of AE reports. The quality and completeness of the reports impacted the DILI assessments, validating previous perceptions identified during the analysis of the combination venetoclax and hepatic failure. AE reports frequently lack information on exclusion of other causes, as well as laboratory results, which complicates the application of RUCAM. Given these limitations, RUCAM should not be used as a standalone diagnostic tool, and it cannot substitute clinical judgement in the context of AE reports.

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Leveraging Machine Learning and Artificial Intelligence in a Novel Multi-Agent Intelligent System for Pharmacovigilance: Early-Stage Development Study

Payam Peymani[1], Amir Hossein Alizadeh Bahmani[2]

[1]*Children's Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg, Canada.* [2]*Precision Medicine Devision, Department of Pulmonary Medicine, Amsterdam UMC location, University of Amsterdam, Amsterdam, Netherlands*

Introduction: Despite rigorous pre-market testing, limitations in clinical trial size and duration often leave rare adverse drug events (ADEs) and reactions (ADRs) undetected. Traditional post-marketing surveillance systems are plagued by low reporting rates and limited accuracy, hindering the timely identification of unknown ADRs. Medication errors (MEs) further exacerbate this challenge, leading to a significant global healthcare burden.

Aim/Objective: The growing availability of electronic patient records (EPRs) across healthcare institutions presents an opportunity to leverage machine learning (ML) and artificial intelligence (AI) for a more effective pharmacovigilance system. This feasibility study evaluates the global potential of a novel Multi-Agent Intelligent System (MAIS) powered by ML and AI to function as a Clinical Decision Support System (CDSS). We focus on Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Metformin, commonly used medications with known safety concerns.

Methods: Our new MAIS leverages AI to analyze vast amounts of real-world patient data, including demographics, lab results, medication history, and physician notes. It employs data mining and machine learning to identify potential ADEs and ADR signal pairs, facilitating proactive and data-driven decision-making for healthcare providers. The pilot study will be implemented in healthcare settings located in Switzerland and the Netherlands. The anonymized patient data will be analyzed to assess the effectiveness of MAIS in real-time ADE detection and prevention. Additionally, clinician feedback on the usability and impact of the MAIS will be collected through surveys and interviews.

Results: This proof-of-concept study suggests promising initial benefits for pharmacovigilance:

-Increased Detection: Preliminary findings show the system may improve detection of acetaminophen overdose and drug-induced liver injury by 3% and 5% respectively, requiring no additional intervention beyond its use.

-Improved Decision-Making: By providing objective, data-driven support, the system can assist healthcare professionals in making more accurate diagnoses and treatment plans.

-Enhanced Patient Safety: Proactive identification of potential ADEs and medication errors can potentially decrease patient mortality and morbidity risks, as well as shorten hospital stays.

Conclusion: This Early-Stage Development study represents a critical step towards a global AI-driven pharmacovigilance system. By leveraging the comprehensive capabilities of Novel MAIS, the study aims to significantly reduce the burden of AI-detectable ADEs in vulnerable populations worldwide, ultimately improving patient safety and healthcare outcomes.

Future Directions:

-Regionalization: Developing algorithms tailored to specific medications and populations (seniors, pregnant women, pediatrics) across diverse regions (e.g., North America, Europe, Asia).

-High-Risk Targeting: Prioritizing medications with frequent ADE/ME reports in each region.

-Real-World Validation: Implementing the system in hospitals across various regions to rigorously evaluate its accuracy and precision in real-world settings.

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Dosing Instructions on Prescription to Improve Medication Safety—A Cross Sectional Study on German Community Pharmacists

Natalie Parrau[1], Aleksandra Schwarzrock-Fabian[1], Leonard Freudewald[1], André Said[1], Martin Schulz[1,2]

[1]*Drug Commission of German Pharmacists (AMK), Berlin, Germany.* [2]*Department of Pharmacy, Freie Universität Berlin, Berlin, Germany*

Introduction: Dosing errors represent the most frequently reported medication errors in the outpatient sector [1]. To address this issue, prescriptions in Germany must feature specific dosing instructions (e.g. "1-0-1") by law since November 1st, 2020 [2]. However, in case patients already receive (standardized) medication lists, the abbreviation "Dj" (dosing instruction available: yes) can be displayed on prescription.
Aim/Objective: To evaluate German pharmacists' perceptions on the current proportion of written dosing instructions on prescription and its effects on medication safety and to determine, if dosing instructions on prescription help to identify (potential) medication errors.
Methods: The Drug Commission of German Pharmacists (AMK) surveyed its nationwide network of 588 reference community pharmacies between September 25th and October 9th, 2023, using the LamaPoll® online survey tool.
Results: A total of 318 community pharmacies participated: response rate of 54.1%. Notably, within the context of the last three months prior to the survey, pharmacies estimated that a median of 90% of prescriptions contain the required dosage information, of which 50% of the prescriptions include "Dj" and 40 % featured specific dosing instructions.
Nearly 44 % of the respondents perceived a (strong) improvement of medication safety since specific dosing instructions e.g. facilitate patient counseling. However, 53% of pharmacists estimated that medication safety has only improved to some extent or not at all, because outdated or inconsistent dosing information necessitate additional consultation efforts to address patient concerns. Moreover, pharmacists considered "Dj" as not specific enough and a supposed medication plan or (written) dosage instructions for patients were, in fact, missing.

Furthermore, a total of 78% of respondents stated that dosing information facilitated the identification of potential medication errors, such as over-/underdosing, lack of divisibility of the prescribed dosage form or incorrect time of administration.
Conclusion: The AMK reference pharmacies confirm that accurate dosing instructions on prescription emerge as a valuable tool for improving patients' adherence and for the detection of potential medication errors. However, pharmacists consider the use of "Dj" as not useful to improve medication safety.
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Celecoxib-Induced Leucocytoclastic Vasculitis: A Case Report

Bouraoui OUNI[1], Neila FATHALLAH[1], Raja GHZEL[2], Raoudha SLIM[1], Malek SASSI[3], Nedia GHIRIANI[4], Ilyes TURKI[5], Nesrine BenSayed[6]

[1]*Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia.* [2]*Emergency department, Ibn Eljazzar Hospital, Kairouan, Tunisia.* [3]*Faculty of pharmacy, University of Monastir, Monastir, Tunisia.* [4]*Dermatology department, Farhat Hached hospital, Sousse, Tunisia.* [5]*Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia.* [6]*Hematology department, Farhat Hached hospital, Sousse, Tunisia*

Introduction: Drug-induced leukocytoclastic vasculitis (LCV), accounting for 10%, is a challenging diagnosis that had to be distinguishable from idiopathic, infective, autoimmune-mediated, or paraneoplastic vasculitis. It's mainly related to the use of beta-lactams and non-steroidal anti-inflammatory drugs (1). Here, we report a case of leucocytoclastic vasculitis induced celecoxib.
Aim/Objective: We report a case of leucocytoclastic vasculitis induced celecoxib.
Methods: Not applicable.
Results: A 58-year old male with a medical history of type 2 diabetes treated with glimepiride. For an acute renal colic, he received celecoxib. Nearly ten days later, the patient presented to the emergency department with painful symmetrically distributed purpuric papules and maculas with fever and fatigue. He was hospitalized in dermatology department and the diagnosis of celecoxib-induced vasculitis was suspected. Celecoxib was immediately discontinued. Physical examination was unremarkable, except for purpuric papules and maculas in lowers limbs. All biological tests performed were with normal ranges. There was no evidence of other infections, connective tissue disorders, hematological disorders, or malignancy. Skin biopsy performed and revealed a leucocytoclastic vasculitis (LCV) with perivascular inflammatory cells, and extravasation of erythrocytes. Direct immunofluorescence study was negative. Results of microbiologic and auto-immunity tests ruled out other causes of LCV. The patient was treated with corticosteroide and antihistaminic drug. The patient fully recovered from the reaction with no apparent complications and he was discharged later. Drug-induced LCV was retained in view of the suggestive temporal relationship and the exclusion of differential etiologies. According to the Naranjo probability scale; causality relationship of celeoxib was probable (Naranjo's score 6) (2).
Conclusion: Celecoxib is known to induce LCV. Early diagnosis and treatment can reduced morbidity and mortality.
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Atorvastatine Induced Acute Pancreatitis: Case Report

Bouraoui OUNI[1], Neila FATHALLAH[1], Raja GHZEL[2], Raoudha SLIM[1], Malek SASSI[3], Imen AKKARI[4], Ilyes TURKI[5], Nesrine BEN SAYED[6]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, sousse, Tunisia. [2]Emergency department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [3]Faculty of pharmacy, University of Monastir, Monastir, Tunisia. [4]Gastroenterology department, Farhat Hached hospital, sousse, Tunisia. [5]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [6]Hematology department, Farhat Hached hospital, sousse, Tunisia

Introduction: Statins included atorvastatine are commonly used for the treatment of hyperlipidemia. They are generally well tolerated, except for the risk of myopathy and liver injury (1). We report a case of acute pancreatitis induced by atorvastatin therapy.
Aim/Objective: To highlight the importance of recognizing acute pancreatitis as a possible adverse event associated with atorvastatine so that clinicians will be more aware of this potential life-threatening adverse reaction.
Methods: Not applicable.
Results: A 53-year-old man, with a history of diabetes, hypertension treated with metformine and captopril and had been recently diagnosed hyperlipidiemia and therapy with atorvastatine was started. Nearly 2 months later, the patient developed acute abdominal pain radiated to the back, nausea with no fever. Biology testing objected an elevated serum lipase levels of 468UI/L (NL≤52 UI/L). Serum bilirubin alongside with liver enzyme levels were within normal limits. Serum pancreatic enzymes were within normal limits the day before atorvastatine initiation. The diagnosis of drug induced acute pancreatitis was suspected. Abdominal computed tomography revealed a normal liver, absence of gallstones in the bile duct or biliary structures, but showed enlarged and oedematous pancreas (stade C). Accordingly, the patient denied alcohol use. The patient received intravenous fluide and fasting advised. Because no etiology of pancreatitis was found, the diagnosis of acute pancreatitis induced by atorvastatine was retained. Atorvastatine was discontinued and abdominal pain was decreased as well as serum lipase returned to normal level (48 UI/l). Viral serology (mycoplasme, viral hepatitis, CMV, EBV) were negative and ruled out infectious etiology. The patient fully recovered from the reaction with no apparent complications and he was discharged later. According to the Naranjo probability scale for adverse drug reaction (ADR), pancreatitis-induced by atorvastatine was probable (score of 6) (2).
Conclusion: Physicians should be aware that atorvastatine could induce acute pancreatitis.
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Anaphylactic Shock Induced by Infliximab with Positive Skin Test: A Case Report

Bouraoui OUNI[1], Neila FATHALLAH[1], Raja GHZEL[2], Raoudha SLIM[1], Malek SASSI[3], Imen AKKARI[4], Ilyes TURKI[5], Nesrine BEN SAYED[6]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Emergency department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [3]Faculty of pharmacy, University of Monastir, Monastir, Tunisia. [4]Gastroenterology department, Farhat Hached hospital, Sousse, Tunisia. [5]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [6]Hematology department, Farhat Hached hospital, Sousse, Tunisia

Introduction: Treatment with the anti-tumour necrosis factor alpha chimeric monoclonal antibody infliximab is highly effective in the treatment of Crohn's disease. Generally, infliximab has been tolerated well, but severe side effect to infliximab, such as anaphylactic shock, is small; nevertheless, if they do occur, they are life-threatening (1). We report a case of an anaphylactic shock induced by infliximab in a 17-year-old male with long-standing Crohn's disease.
Aim/Objective: We report a case of an anaphylactic shock induced by infliximab in a 17-year-old male with long-standing Crohn's disease.
Methods: Not applicable.
Results: A 17-year-old male patient with medical history of ileal Crohn's disease treated at the beginning with conventional immunosuppressive agents (corticosteroid, and azathioprine). In June 2023, the patient had been treated with infliximab (intravenous infusion). Before the first infusion (200 mg/500ml), the patient received premedication by corticosteroid and his clinical exam and biological test were normal (blood pressure: 110/60mmHg). Ten minutes after the end of infusion, the patient developed dyspnea, agitation, stridor and generalised urticarial eruption. The patient's oxygen saturation was 71%, her blood pressure was 60/36 mmHg with tachycardia. The diagnosis of anaphylactic shock induced by infliximab was retained. The patient received hydrocortisone, adrenaline and fluids. Thereafter, the patient symptoms improved and he fully recovered without apparent complications. Skin test with suspected drug diluted was performed and showed positive results associated to pruritis and malaise sensation. According to the Naranjo probability scale for adverse drug reaction (ADR), infliximab-induced anaphylactic shock was probable (score of 8) (2).
Conclusion: In the future severe anaphylactic reactions should be described concerning dose, if the reaction ocurred in the first or subsequent infusions, severity of symptoms and treatment in order to establish criteria for the prompt identification and treatment of this rare but life-threatening condition.
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Rifampicin Induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) with Positive Rechallenge

Bouraoui OUNI[1], Neila FATHALLAH[1], Raja GHZEL[2], Raoudha SLIM[1], Malek SASSI[3], Awatef AZZEBI[4], Ilyes TUKI[5], Nesrine BEN SAYED[6]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Emergency department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [3]Faculty of pharmacy, University of Monastir, Monastir, Tunisia. [4]Nephrology department, Sahloul hospital, Sousse, Sousse, Tunisia. [5]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [6]Hematology department, Farhat Hached hospital, Sousse, Tunisia

Introduction: DRESS syndrome is defined as drug-induced hypersensitivity syndrome with rash, eosinophilia, and systemic symptoms. This syndrome is mostly associated with anticonvulsants, antibacterial and anti-inflammatory drugs (1). Antituberculosis drugs can cause a cutaneous syndrome in the form of mild rashes, pruritus, and on very rare occasions DRESS syndrome **(2)**. We present a case report of DRESS syndrome in an 34-year-old women patient induced by rifampicin with positive rechallange.
Aim/Objective: We describe a case of rifampicin-induced DRESS with positive rechallange.
Methods: Not applicable.
Results: A 34-year-old woman with a medical history of lupus and Sjogren syndrome (all diseases were stable), was hospitalized in internal medicine for cervical lymph node tuberculosis confirmed by ganglionar biopsy. She was treated with isoniazid, rifampicin, pyrazinamide, and ethambutol (fixed dose combination). Pretherapeutic biological test were within normal range. Ten days later, the patient presented a generalised maculopapular rash, fever, and fatigue. Initial laboratory tests were as follows: hyperleucocytosis ($18x10^3/\mu L$), hypereosinophilia (5%, 900), activated lymphocyte in blood smear, increase transaminases (AST:168 U/L, ALT: 130 U/L), total bilirubin 28 mg/dl (NR: 0.2-1), alkaline phosphatase (ALP) 230 U/L (NR<140), gamma GT (156 U/L <50). Serological tests for viral infections, including hepatitis A, B, and C, Epstein-Barr virus, and cytomegalus virus were negative. DRESS syndrome to antituberculosis drugs was suspected. All antituberculosis drugs were discontinued and the patient was treated with corticosteroid. All clinical and biological symptoms were improved after discontinuation of antituberculosis drugs and one week of corticosteroid therapy. Skin biopsy performed and confirmed the diagnosis of DRESS syndrome. Reintroduction of antituberculosis drugs was performed one month later and only the rifampicin reintroduction was positive. Even, the protocol of rifampicin desensitization has failed. The diagnosis of DRESS syndrome to rifampicin was retained. According to the Naranjo probability scale for adverse drug reaction (ADR), pancreatitis-induced by atorvastatine was definite (score of 9) (3).
Conclusion: Rifampicine is known to induce DRESS syndrome. Early diagnosis and treatment can reduced morbidity and mortality.
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Fluoroquinolones Use and Risk of Hospitalization for Spontaneous Pneumothorax: A Nationwide Case-Time-Control Study

Anne Bénard-Laribière[1], Elodie Pambrun[1], Serge Kouzan[2], Jean-Luc Faillie[3], Julien Bezin[4], Antoine Pariente[4]

[1]Univ. Bordeaux, INSERM, BPH, team AHeaD, U1219, Bordeaux, France. [2]Pulmonary Department, Centre Regional Hospital, Chambery, France. [3]Univ Montpellier, INSERM, Desbrest Institute of Epidemiology and Public Health; CHU Montpellier, Department of Medical Pharmacology and Toxicology, Montpellier, France. [4]Univ. Bordeaux, INSERM, BPH, team AHeaD, U1219; CHU Bordeaux, Clinical Pharmacology Unit, INSERM, U1219, Bordeaux, France

Introduction: Fluoroquinolones can cause severe collagen-associated adverse effects, including tendon rupture or aortic aneurysm or dissection. Other connective tissues could be affected including that of lung, potentially exposing to a risk of pneumothorax.
Aim/Objective: The aim this study was to investigate the association between fluoroquinolones use and the risk of spontaneous pneumothorax.
Methods: Within the SNDS, we performed a case-time-control study using amoxicillin as an active comparator to control for potential indication bias. Cases were inpatients aged $\geq$18 hospitalized for spontaneous pneumothorax from 2017 to 2022 and exposed to fluoroquinolones or amoxicillin within 180 days before admission (246 fluoroquinolone; 3,316 amoxicillin). Adjusting for time-varying confounders, association Odds Ratio (OR) was assessed comparing for each case antibiotic exposure between the risk period (days -30 to -1) and three earlier reference periods (days -180 to -151, -150 to -121, -120 to -91). To control for exposure-trend bias, a similar analysis was performed in patients free of the event and individually matched to cases on sex, age, COPD history and calendar time (1,846 time-trend controls for fluoroquinolone; 32,494 for amoxicillin). The associations to the risk of pneumothorax were finally corrected for the exposure-trend estimations.
Results: Of the 246 cases exposed to fluoroquinolones (63.8% men; mean age, 43.0$\pm$18.4 years), 63 were exposed in the 30-day risk period preceding pneumothorax and 128 in the reference periods. Of the 3,316 amoxicillin cases (72.9% men; mean age, 39.4$\pm$17.6 years), 1,210 were exposed in the risk period and 1,603 in the reference ones. OR adjusted for exposure-trend and covariates was 1.59 (95% CI: 1.14-2.22) for fluoroquinolones and 2.25 (2.07-2.45) for amoxicillin.
Conclusion: Both fluoroquinolones and amoxicillin increased spontaneous pneumothorax risk, but the amoxicillin association equaled or exceeded fluoroquinolones, suggesting no causal role but a probable indication bias. These reassuring results also highlight the need to use

active comparator in self-controlled design when an indication bias appears possible.

References

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Can We Ask ChatGPT About Drug Safety? Appropriateness of ChatGPT Responses to Questions about Drug Use and Adverse Reactions

Antoine Pariente[1], Francesco Salvo[1], Virginie Bres[2], Jean-Luc Faillie[3]

[1]Univ. Bordeaux, INSERM, BPH, team AHeaD, U1219; CHU Bordeaux, Clinical Pharmacology Unit, Bordeaux, France. [2]CHU Montpellier, Department of Medical Pharmacology and Toxicology, Montpellier, France. [3]Univ Montpellier, INSERM, Desbrest Institute of Epidemiology and Public Health; CHU Montpellier, Department of Medical Pharmacology and Toxicology, Montpellier, France

Introduction: In France, the network of pharmacovigilance experts who inform the public and healthcare professionals about drug safety is in such high demand that it is essential to find ways to safely automate some tasks currently performed by humans. ChatGPT, recently launched as a prototype artificial intelligence (AI) chatbot, is able to suggest answers to questions and write text according to a set of given constraints.

Aim/Objective: To investigate the usefulness of ChatGPT as a tool to assist in the writing of responses to drug safety questions.

Methods: Between February and March 2023, we randomly selected 60 questions received and answered by two French pharmacovigilance regional centers by the end of 2021, the period of ChatGPT v3.5 training. These questions comprised 30 from patients and 30 from healthcare professionals, covering various categories including potential ADRs, drug use during pregnancy and breastfeeding, and drug-drug interactions. The responses provided by ChatGPT were compared to those given by pharmacovigilance experts, serving as the gold standard. Two pharmacovigilance experts independently rated each ChatGPT response for reliability.

Results: Overall, 56.7% of ChatGPT responses were deemed reliable (38.3% fully; 18.3% rather). Reliability was marginally higher for patient questions compared to healthcare professional inquiries (overall reliability: 63.3% [95% CI: 43.9-80] vs. 50% [95% CI: 31.3-68.7]; full reliability: 46.7% [95% CI: 28.3-65.7] vs. 30% (95% CI: 14.7-49.4]) (Figure 1). Responses regarding potential ADRs exhibited higher reliability compared to those regarding pregnancy (60.5% [95% CI: 43.4%; 76%] vs. 50% [95% CI: 24.7; 75.4]), with similar full reliability rates (36.8% [95% CI: 21.8-54] vs. 37.5% [95% CI: 15.2-64.6]). Notably, reliability seemed higher for patients' unspecific questions about ADRs and patients' specific questions not related to ADRs.

Conclusion: ChatGPT's strength lies in summarizing information available from various sources, rather than handling intricate queries directly [1, 2]. Similar findings have been reported in previous studies focusing on complex question settings in hospital contexts [3, 4]. However, these results are exploratory, based on a limited sample size, and warrant further investigation at a broader scale. If validated, ChatGPT could serve as a valuable tool for drafting responses, subsequently validated by experts, in the perspective of contributing to care. Nonetheless, relying solely on AI-generated responses remains unacceptable due to various concerns raised by both academic and industry experts, healthcare professionals, institutions, and patients [5, 6]. Despite the study's limitations, such as its small sample size, the use of real-life questions processed by pharmacovigilance centers enhances its relevance. Moreover, subsequent iterations of ChatGPT might yield different results. Therefore, continual evaluation of AI-based tools' performance is imperative, given their evolving nature and the dynamic nature of the data they analyze. Ultimately, human validation remains crucial for any health-related response generated by AI-based tools.

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Vancomycine Infusion Induced Anaphylactic Shock: A Case Report

Bouraoui OUNI[1], Neila Fathallah[1], Awatef AZZEBI[2], Raoudha SLIM[1], Malek SASSI[3], Imen AKKARI[4], Ilyes TURKI[5], Nesrine BEN SAYED[6]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Nephrology department, Sahloul hospital, Sousse, Tunisia. [3]Faculty of pharmacy, University of Monastir, Monastir, Tunisia. [4]Gastroenterology department, Farhat Hached hospital, Sousse, Tunisia. [5]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [6]Hematology department, Farhat Hached hospital, Sousse, Tunisia

Introduction: Vancomycin is a glycopeptide antibiotic exhibiting bactericidal activity against gram-positive cocci, as well as methicillin-resistant Staphylococcus aureus (MRSA), but it is associated with many adverse effects such as nephrotoxicity, ototoxicity, gastrointestinal disturbances, blood disorders, and two types of hypersensitivity reactions—an anaphylactoid reaction known as "red man syndrome" and anaphylaxis (1).

Aim/Objective: We report a case of 3-year-old female child who developed a vancomycin-induced anaphylactic shock.

Methods: Not applicable.

Results: A 3-year-old female child with medical history of acute myeloblastic leukemia treated with conventional chimiotherapy. At the end of course of chemotherapy, the patient experienced fever and her complete blood count showed severe neutropenia. The patient was admitted in isolation room and a treatment with intraveinous vancomycine was started. At the end of vancomycine infusion, the patient immediately experienced flushing of her face and cutaneous itching followed by shortness of breath with chest pain, severe hypotension (60/40 mmHg) and tachycardia. The diagnosis of anaphylactic shock induced by vancomycine was retained and it was well managed with adrenaline, corticosteroid and fluid infusion. Vancomycine was contra-indicated and the patient was switched to clindamycin. Because the seriousness of the reaction, patient's familly refused to perform skin test. According to the Naranjo probability scale for adverse drug

reaction (ADR), vancomycine-induced anaphylactic shock was probable (score of 6) (2).

Conclusion: In view of life threatening anaphylactic/anaphylactoid reactions developing after vancomycine injection, high caution is required especially in patients with history of hypersensitivity reactions.

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Assessment of Residents of Medicine Level of Knowledge in Pharmacovigilance (Faculty of Medicine of Sousse, Tunisia)

Bouraoui OUNI[1], Nesrine BEN SAYED[2], Awatef AZZEBI[3], Fatma HARRATH[1], Raoudha SLIM[1], Med Ali KHALIFA[4], Ilyes TURKI[5], Neila FATHALLAH[1]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Hematology department, Farhat Hached hospital, Sousse, Tunisia. [3]Nephrology department, Sahloul hospital, Sousse, Tunisia. [4]Orthopaedic surgery, Sahloul hospital, Sousse, Tunisia. [5]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia

Introduction: Pharmacovigilance is a discipline aimed at monitoring, evaluating, managing, and preventing the adverse effects resulting from the use of medications. It is crucial in everyday medical practice and contributes to ensuring patient safety by identifying and managing the risks associated with drugs (1).

Aim/Objective: To assess the level of knowledge among residents of medicine in Sousse (Tunisia) regarding pharmacovigilance.

Methods: A cross-sectional observational study was conducted to evaluate the knowledge of residents of medicine (across all specialties) in pharmacovigilance. Data were collected using an anonymous questionnaire that included personal and professional information, knowledge about pharmacovigilance. Statistical analysis was performed using the SPSS software, and a literature search was conducted to support the study.

Results: The survey conducted among 511 residents of medicine revealed that 65% were females and 35% were males. The most common specialty type was medical specialty with 36.6% of participants, followed by family medicine (34.6%) and surgical specialties (28.8%). Regarding the residents' knowledge of pharmacovigilance, 87.1% had heard about it during their medical studies. The majority (83%) accurately defined pharmacovigilance as the detection, evaluation, understanding, and prevention of adverse effects. However, almost all residents were not aware of the Tunisian pharmacovigilance system (53.2%) or the Sousse Regional Pharmacovigilance Center (30.1%). Regarding the residents' knowledge of pharmacovigilance, 61.4% knew that reporting adverse effects was mandatory, but only 29.2% were aware of the healthcare professionals involved in this reporting. The majority of residents were unfamiliar with causality assessment methods in pharmacovigilance (97.3%) and the timeframe for reporting a serious adverse effect (96.5%). Concerning the reporting of adverse effects, most residents knew they should report all types of adverse effects but believed they didn't report enough (83.6%). The majority of residents reported adverse effects to the national/regional pharmacovigilance center (91.2%).

Conclusion: Our results underscore the necessity to enhance pharmacovigilance training and awareness among healthcare professionals in training.

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Serious Acute Pancreatitic Reaction in the Context of Misuse of Dulaglutide for Weigh Loss: A Case Report

Louise Cuvelier[1], Elise Lecointre[1], Nicole Hastier-Gouin[1], Nathalie Massy[2], Jean-Luc Faillie[3], Pascal Le Roux[1]

[1]Le Havre Hospital, Department of Pediatrics, Montivilliers, France. [2]CHU Rouen, Pharmacovigilance Regional Center, Rouen, France. [3]Univ Montpellier, INSERM, Desbrest Institute of Epidemiology and Public Health; CHU Montpellier, Department of Medical Pharmacology and Toxicology, Montpellier, France

Introduction: Dulaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated in the management of type 2 diabetes in the form of subcutaneously weekly injection. Other GLP-1 RAs (semaglutide, liraglutide) are also authorized for the indication of obesity. Because of their anorectic effect, GLP-1 RAs are misused for weight loss outside their official indications.

Aim/Objective: To increase awareness regarding the pancreatic safety of GLP-1 RA in non-diabetic, non-obese individuals.

Methods: We report a case of serious acute pancreatitic reaction occurring in the context of misuse of dulaglutide by a non-diabetic non-obese young female.

Results: A 17-year-old girl (weight: 62.8 kg, height: 1.55 m, BMI: 25.8), with no prior psychiatric or medical history except for a urinary infection, self-administered a subcutaneous injection of 1.5 mg of dulaglutide at school with a friend. She obtained the medication from her mother, who was prescribed dulaglutide 1.5 mg once weekly for type 2 diabetes. After 24 hours, she presented with uncontrollable vomiting and intense abdominal pain, which began 4 hours post-administration of the drug.

Clinical examination revealed epigastric pain without abdominal contracture. There was no dyspnea, no fever, no diarrhea. Glycemia was 4.5mmol/L. She vomited every time she ate. After 48 hours, serum lipase was at 343 U/L, liver function test and C-reactive protein were normal, there were 9.69 G/L neutrophils. Abdominal ultrasounds showed a 4 millimeters polyp without peritoneal effusion or cholelithiasis. The rest of the ultrasound was normal. The patient fasted and was infused with polyionic G5% 1500 mL. After 24h, the pain was releaved and she was able to begin low-fat diet on the 3rd day. On the 4th day, lipase decreased to 202 U/L and she was discharged on 5th day. The medical team reported this effect as acute pancreatitis.

Conclusion: The chronology and semiology of this case are suggestive of a dulaglutide-induced acute pancreatitis. Pancreatitis is a known adverse reaction of GLP-1RA used in type 2 diabetic patients but this is the first reported case of serious acute pancreatitic reaction in a context of misuse of dulaglutide in a non-diabetic non-obese young patient.

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Causes of Under-Reporting of Adverse Events and Solution According to Residents of Medicine (Faculty of Medicine of Sousse, Tunisia)

Bouraoui OUNI[1], Nesrine BEN SAYED[2], Fatma Harrath[1], Imen AKKARI[3], Awatef AZZEBI[4], Med Ali KHALIFA[5], Ilyes TURKI[6], Neila FATHALLAH[1]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Hematology department, Farhat Hached hospital, Sousse, Tunisia. [3]Gastroenterology department, Farhat Hached hospital, Sousse, Tunisia. [4]Nephrology department, Sahloul hospital, Sousse,, Sousse, Tunisia. [5]Orthopaedic surgery, Sahloul hospital, Sousse, Tunisia. [6]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia

Introduction: Pharmacovigilance is a discipline aimed at monitoring, evaluating, managing, and preventing the adverse effects resulting from the use of medications. Reporting system of adverse drug reactions (ADRs) is fundamental to drug safety surveillance but under-reporting is its major limitation (1).
Aim/Objective: Described causes of under-reporting of adverse events and solution according to Residents of Medicine (Faculty of Medicine of Sousse, Tunisia).
Methods: A cross-sectional observational study was conducted to describe causes of under-reporting of adverse events and Solution according to Residents of Medicine (Faculty of Medicine of Sousse, Tunisia). Data were collected using an anonymous questionnaire included reasons for underreporting adverse effects, and suggested corrective actions. Statistical analysis was performed using the SPSS software, and a literature search was conducted to support the study.
Results: Among 750 residents were working in the Sousse region. Only 511 participated in our study, with a participation rate of 68%. The most common specialty type was medical specialty with 36.6% of participants, followed by family medicine (34.6%) and surgical specialties (28.8%).
Table 1 represents the main reasons for residents' non-reporting of adverse effects. we have suggested a few ways of improving the reporting of undesirable effects:

Causes of under-reporting of adverse reactions by residents	Headcount	Percentage (%)
Because adverse reactions are frequent	36	7
Because adverse reactions are benign	**126**	**24.7**
Because adverse reactions are known	**115**	**22.5**
Because residents don't know what to do	**92**	**18**
Because it takes too long	63	12.3
Because residents feel that reporting ADRs is not their role	9	1.8
Because residents have not encountered an ADRs	23	4.5
Because imputability is difficult to prove	33	6.5

The strategy most suggested concerned the availability of adverse event reporting forms (85.9%), followed by training for all healthcare professionals (85.7%), then awareness-raising for all healthcare professionals (80.4%) and systematic feedback from the CRPV for all adverse event reports (also 75.9%), then easy access to information on adverse events (69.9%). Secondly, residents also suggested simplifying the procedure for reporting adverse reactions to the hospital (48.5%), a reporting system on a Smartphone application (26.6%) and finally the appointment of a pharmacovigilance referent at the hospital (21.7%).

Conclusion: Our results underscore the necessity to enhance pharmacovigilance training and awareness among healthcare professionals in training.
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Allergy-Like Nocebo Events with COVID-19 Vaccination are Associated With Age, History Of allergy, Vaccine Type and Poor Perception of Effectiveness

Virginie Bres[1], Najah Ben Fadhel[2], Raphael Trouillet[3], Guillaume Broc[3], Anca Chiriac[4], Jean-Luc Faillie[5]

[1]CHU Montpellier, Department of Medical Pharmacology and Toxicology, Montpellier, France. [2]Department of Clinical Pharmacology, University Hospital of Monastir, Faculty of Medicine of Monastir, University of Monastir, Monastir, Tunisia. [3]Department of Clinical Psychology, EPSYLON laboratory, Paul Valéry University Montpellier 3, Montpellier, France. [4]CHU Montpellier, Division of Allergy, Department of Pulmonology, Montpellier, France. [5]Univ Montpellier, INSERM, Desbrest Institute of Epidemiology and Public Health; CHU Montpellier, Department of Medical Pharmacology and Toxicology, Montpellier, France

Introduction: Allergy to COVID-19 vaccine is considered extremely rare.[1] However, allergy-like symptoms have been frequently reported by patients, and COVID-19 vaccine trials have shown significant rates of nocebo responses.[2,3] This raises the question of whether adverse effects of vaccination could largely be due to the nocebo effect rather than the vaccine itself.
Aim/Objective: This study aimed to characterize nocebo responses and their associated factors following COVID-19 vaccination.
Methods: We conducted a case-control study using pharmacovigilance records from a regional pharmacovigilance centre in France, supplemented by a cross-sectional self-administered questionnaire study. Patients reporting allergy-like symptoms without fever and without a diagnosis of anaphylaxis were considered nocebo cases. Controls reported reactogenic or localised reactions. Data on demographics, medical history, vaccinations and psychological factors were collected and analysed using multivariate logistic regression to identify risk factors associated with nocebo effects.
Results: We included 1038 patients: 320 nocebo cases (mean age 49.7 [SD: 16.2], 75.3% female) and 718 controls (mean age 48.5 [SD: 15.1], 75.3% female). Allergy-like symptoms in cases were predominantly cutaneous (71.8%) and respiratory (38.8%), occurring immediately in 38.1% and after the first dose in 43.4%. In multivariate analysis, nocebo responses were positively associated with age (OR 1.01, 95% CI: 1-1.02, p = 0.13), history of allergy (OR 1.62, 95% CI: 1.22-2.16, p = 0. 001) and BNT162b2 mRNA vaccine (Comirnaty®) (OR 1.60, 95% CI: 1.20-2.14, p = 0.001) and negatively correlated with the perceived vaccine effectiveness score (OR 0.92, 95% CI: 0.87-0.97, p = 0.002).
Conclusion: This study suggests that the nocebo effect differs according to the type of vaccine and is more common in older people, those with a history of allergy, and those with a poorer perception of vaccine effectiveness. The influence of these clinical and psychological factors on the nocebo effect needs to be further confirmed in order to better understand this phenomenon.
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Unlocking Safety Insights: Integrating Pharmacovigilance and Patient Support Program Data

Victor Gitman[1], Ela Bogoridov[1], Roopa Bhangui[1], Sofija Spasojevic[1], Julia Paiva[1], Aphrodite Stravropoulos[1], Kocho Fitovski[2]

[1]Hoffmann-La Roche Limited, mississauga, Canada. [2]F. Hoffmann-La Roche, Basel, Switzerland

Introduction: Patient support programs (PSPs) are solutions developed by Market Authorization Holders (MAHs) to provide access to treatment and support patients throughout their treatment journey [1]. These programs facilitate interactions between patients, healthcare professionals (HCPs), and the program itself resulting in the generation of data. This data can be pivotal for understanding the real-world experiences of patients particularly concerning safety topics of importance.
Aim/Objective: This review highlights an approach to leveraging data from PSPs and linking it with safety data from the MAH safety database (Roche Global Safety Database). It emphasizes the unique benefits of integrating pharmacovigilance (PV) and PSP data to meet the needs of patients and HCPs.
Methods: A series of descriptive secondary data use studies were conducted by linking individual case safety reports associated with the suspect drug ocrelizumab (OCREVUS®) from the Roche Global Safety Database to data from the Canadian PSP, COMPASS, using a unique patient ID. Key data points included demographics (age, sex), therapy details, adverse event terms, event seriousness, and case specifics. All patients consented to their data being shared and potentially used in an aggregate anonymized form for publication. The analysis was primarily descriptive as the data type and source precluded inferential statistics.
Results: Roche Canada's application of this methodology has addressed three specific patient needs to date. The first analysis evaluated pregnancy and fetal outcomes in women with Multiple Sclerosis (MS) treated with ocrelizumab (OCREVUS®), showing no increased risk of congenital anomalies among 107 maternal exposures [2]. The second assessment reported on a wearing-off effect in MS patients treated with ocrelizumab (OCREVUS®) and found that it was rarely reported in COMPASS (1.12%) with the majority of patients continuing treatment post reporting (87.6%) [3]. The third analysis, incorporated data from three distinct datasets: a non-interventional post-authorization safety study (CONFIDENCE), a German PSP (trotz ms), and the Canadian PSP (COMPASS) to characterize the safety of ocrelizumab (OCREVUS®). No new or unexpected signals were observed in any of the datasets [4].
Conclusion: Understanding how to effectively integrate and leverage PSP and safety data can optimize patient outcomes and enable evidence-based treatment decisions. Key limitations of the methodology include the varying quality of AE reports and PSP data, and the potential for under-reporting of safety events. MAHs should take into consideration the setup and data collection activities of PSPs as a means to contribute to future evidence needs.

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Suspected Adverse Reactions of Eptinezumab in the Treatment Of Headache: Real-World Data From EudraVigilance Database

Laura Costantino[1], Clizia Argirò[1], Francesca Saullo[2], Valentina Salerno[2], Rita Morrillo[2], Eugenia Daniele[2], Giulia Pingitore[1]

[1]University "Magna Graecia", Catanzaro, Italy. [2]University Hospital "Renato Dulbecco", Catanzaro, Italy

Introduction: Eptinezumab is a recombinant humanized immunoglobulin G1 (IgG1) antibody that binds to α- and β-forms of human calcitonin gene-related peptide (CGRP) ligand. It prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events, neurogenic inflammation and vasodilation, linked to initiation of migraine attacks. Eptinezumab is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.
Aim/Objective: At the moment, only information about eptinezumab is available from pre-registration clinical trials, so the aim of our study was to expand our knowledge in order to be able to complete the drug's safety profile.
Methods: We conducted a descriptive analysis of suspected adverse reactions (SARs) related to eptinezumab identified through the EudraVigilance database [1]. The EudraVigilance system collects reports concerning drugs authorised for the market in the European Union (EU). In this database, SARs related to eptinezumab are described in Individual Case Safety Reports (ICSRs). The number of individual cases, seriousness, gender, age group, number of individual cases by Geographic Origin and type of reported reactions were evaluated.
Results: The number of individual cases identified in EudraVigilance for eptinezumab was 401 (215 serious and 186 nonserious), occurring predominantly in women (333) compared to men (51), and 17 were unspecified cases. The average age of affected patients ranged from 18 to 64 years (74.8 percent). According to EudraVigilance data, 53.6 percent of ICSRs were from the European Economic Area, while 46.4 percent were from the non-European Economic Area. The most frequently reported SARs in descending order are associated with: General disorders and site-related conditions; nervous system disorders; gastrointestinal disorders; respiratory, thoracic and mediastinal

disorders; skin and subcutaneous tissue disorders; infections and infestations; immune system disorders; injuries, poisonings and procedural complications; psychiatric disorders; surgical and medical procedures; cardiac disorders; musculoskeletal and connective tissue disorders; vascular disorders; ear and labyrinth disorders; ocular disorders and benign, malignant and unspecified neoplasms (including cysts and polyps).

Conclusion: The analysis of real-world SARs data for eptinezumab [2] confirms the known safety profile of the drug but, at the same time, suggests further investigation into the link with adverse reactions characterised by the occurrence of tumours, including malignancies. Pharmacovigilance therefore plays a key role in completing the safety profile and taking action to reduce the risks and increase the benefits of medicines.

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Influence of External Factors on Spontaneous Reporting Practices: An Analysis of FAERS Data

Victoria Munoz Goyette[1,2], Camille Goyer[2], Anne-Marie Castilloux[2], Genaro Castillon[2], Yola Moride[2,3]

[1]Faculty of Pharmacy, Universitéde Montréal, Montreal, Canada. [2]YolaRX Consultants, Montreal, Canada. [3]Rutgers The State University of New Jersey, New Brunswick, USA

Introduction: External factors such as media coverage, regulatory safety warnings, adverse event (AE) seriousness, and recency of drugs on the market are known to influence spontaneous reporting trends, crucial for identifying potential drug safety signals (1-4). However, the effects of public health crises like the COVID-19 lockdown (since mid-Mar. 2020) or geopolitical events like Brexit on 01 Jan. 2021 remain unexplored.

Aim/Objective: To explore the trends in the number and types of spontaneous reports before and after (i) the COVID-19 lockdown in the United States (US) and the European Economic Area (EEA), (ii) Brexit in the EEA, and to quantitatively assess the impact of the COVID-19 lockdown on safety signal detection.

Methods: We analyzed spontaneous reports from the US and EEA, dated 01 Jan. 2018 to 26 Dec. 2021, obtained from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). Time series analyses were performed, based on type of reporter (health care professionals [HCP], consumers) and AE seriousness, using interrupted autoregressive integrated moving average (ARIMA) models with step (short-term effect) and ramp (long-term effect) intervention functions. The study also compared reporting odds ratios (RORs) estimated until the start of the pandemic and up to the date of FDA publication for two signals–(i) hypersensitivity to apremilast (end of Sep. 2020) and (ii) diabetic ketoacidosis linked to SGLT2 inhibitors in type 1 diabetic patients (end of Dec. 2020)–to assess potential delays in signal detection due to the COVID-19 lockdown.

Results: Significant and immediate reductions in weekly serious HCP reports of -746 (95% CI: -1,267; -225) in the US, and -1,064 (95% CI: -1,709; -419) in the EEA were present during the first week of lockdown. Similarly analyses showed a significant immediate decrease in weekly serious reports from the EEA of -1,009 (95% CI: -1,509; -509) following Brexit. Additionally, the ROR for SGLT2 inhibitors was significant at the onset of the pandemic.

Conclusion: An immediate decline in the number of weekly spontaneous reports of serious events followed both the COVID-19 lockdown and Brexit. These trends did not revert by the end of their respective study periods. Moreover, the COVID-19 lockdown may have delayed the detection of safety signals. Overall, these findings provide an empirical demonstration of the effects of external factors on spontaneous reporting practices.

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Analysis Of ADRs Detected During a Retrospective Study In a Geriatric Department

Clizia Argirò[1], Laura Costantino[1], Francesca Saullo[2], Valentina Salerno[2], Rita Morrillo[2], Eugenia Daniele[2]

[1]University "Magna Graecia", Catanzaro, Italy. [2]University Hospital "Renato Dulbecco", Catanzaro, Italy

Introduction: The elderly are complex patients due to the high prevalence of multimorbidity and co-morbidity, polypharmacy and physiological changes (especially reduced organ function and changes in body composition), which may alter the pharmacokinetics and/or pharmacodynamics of therapies. This makes the elderly extremely susceptible to the risk of occurrence of adverse drug reactions. Therefore, the geriatric population requires continuous observation. The involvement of the Hospital Pharmacist in the monitoring of therapies can assist healthcare professionals in identifying suspected adverse drug reactions (ADRs) in order to ensure greater patient safety.

Aim/Objective: To analyze therapies in the Geriatrics ward of a hospital in the south of Italy, in order to identify any ADRs occurring during the quarter August-October 2023.

Methods: A retrospective analysis of the medical records of 261 patients admitted from 08/01/2023 to 10/31/2023 was conducted; during data collection, Pharmacist staff discussed suspected adverse reactions with clinicians and nurses, in order to verify whether the criticality identified could be related to the administration of one or more drugs. AIFA (Italian Agency Medicines) form for the healthcare professionals was used for reporting ADRs.

Results: The ADRs reported and inserted by the Head of Pharmacovigilance into the National Pharmacovigilance Network were 13: 8 (61.5%) involved men, 53% were considered to be serious as they caused hospitalization or prolongation of hospitalization; complete resolution of symptoms was achieved in 9 cases (69.2%). All reported ADRs are summarized in Table 1.

Table 1. ADRs reported.

Suspected drugs	ADRs	Seriousness
prednisone, lysine acetylsalicylate, clopidogrel, enoxaparin	melaena	serious
warfarin	melaena, anaemia, increased INR	serious
oxcarbamazepine	hyponatraemia	serious
metoprolol	sinus bradycardia	serious
solifenacin succinate	anuria	serious
spironolactone	hyperkalemia, hypercreatinemia, hyponatraemia	serious
dexamethasone	hyperglycemia	non-serious
piperacillin-tazobactam	urticarial rash	non-serious
ciprofloxacin	elevated transaminases	non-serious

Conclusion: According to literary sources [1, 2], adverse drug reactions have a considerable impact on hospitalizations in the elderly and, in this regard, during our work we found that more than half of the ADRs reported were the cause of a more or less prolonged hospitalization period. By virtue of the complexity of the geriatric patient and the numerous treatments, it is often difficult to establish a probable correlation between a given side effect and a drug therapy; in this delicate context, the Hospital Pharmacist is the healthcare figure best qualified to offer maximum support to medical and nursing staff in identifying and reporting ADRs.

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Analysis of the Risk of Gastrointestinal Bleeding in the Elderly Patient and Evaluation of the Impact of Antithrombotics

Clizia Argirò[1], Laura Costantino[1], Francesca Saullo[2], Valentina Salerno[2], Eugenia Daniele[2], Rita Morrillo[2]

[1]University "Magna Graecia", Catanzaro, Italy. [2]University Hospital "Renato Dulbecco", Catanzaro, Italy

Introduction: The risk of gastrointestinal bleeding is very high in elderly patients, mainly due to the high consumption of anticoagulants and antiplatelet agents, belonging to the same therapeutic class (antithrombotics, ATC B01). Literature studies show that this risk is much higher in patients taking combinations of anticoagulants and antiplatelet agents at the same time, compared with monotherapy [1] (this, has been associated with an increase in hospitalisations [2]).
Aim/Objective: In order to assess the exposure to the risk of gastrointestinal bleeding, to analyse the impact of the B01 class and to check whether there have been hospitalisations caused by gastrointestinal bleeding, the Pharmacist Staff of a hospital in the south of Italy, during a retrospective survey carried out in the Geriatrics ward, analysed the treatment of elderly patients admitted.
Methods: Through consultation of the medical records, the drug therapy taken by the patients at the time of admission was examined. The period considered was from 08/01/2023 to 10/31/2023. Any interactions were analysed using the INTERCheck-WEB® platform and the data were collected and processed using Excel®.
Results: There were 261 patients (130 women and 131 men; mean age 83.4 years). From the analysis of the therapies, 24 subjects (9.2%) were found to be on therapy with an association leading to bleeding in the gastrointestinal tract and, in 95.8% of cases (23 patients), the interaction was caused by an antithrombotic drug. Furthermore, the risk determined by the co-administration of several antithrombotic drugs is relevant since, among the 24 patients at risk, in 41.7% of the cases the interaction is determined by the simultaneous intake of substances belonging to therapeutic class B01. Pharmacists identified two cases of gastrointestinal bleeding that resulted in hospitalisation, and these events were subsequently reported as suspected adverse drug reactions (ADRs). In the first case, an 86-year-old man came to the emergency department for an episode of melaena and rectorrhage at home; the reaction was reported as a suspected adverse reaction to prednisone, lysine acetylsalicylate, clopidogrel and enoxaparin; the second patient (man, 84 years old) was admitted for increased INR values (2.92; reference range > 0.80-1.20<), anaemia and melaena, reported as a suspected adverse reaction to warfarin.
Conclusion: This review reveals the considerable impact that antithrombotics have in determining the risk of gastrointestinal bleeding. Furthermore, it is highlighted that the Hospital Pharmacist, as a drug expert, can support clinicians in identifying clinically relevant severe interactions and can contribute significantly to patient safety by raising awareness of reporting.

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Responding to Reports of Colchicine Fatalities in New Zealand

Maria Storey[1], Susan Kenyon[1], Nevin Zhong[1], Jennifer Lee[2], Michael Tatley[2]

[1]Medsafe, Wellington, New Zealand. [2]University of Otago, Dunedin, New Zealand

Introduction: Medsafe has received several coronial reports of people who died after taking overdoses of colchicine. Colchicine is widely used in New Zealand (NZ) due to the high prevalence of gout.
Aim/Objective: To investigate whether any actions can be taken to reduce the risk of inappropriate use of colchicine.
Methods: Colchicine reports to the NZ Centre for Adverse Reactions Monitoring (CARM) were reviewed to investigate whether any risk factors could be identified. The NZ Poisons Centre was asked for a summary of their information.
A project team was assembled to discuss potential actions that could be taken by different sectors of the community to reduce the risk of inappropriate colchicine use.

The project team recommended:

- Reminders to healthcare professionals of the risks with colchicine and the importance of informing patients on appropriate storage and disposal.
- Information to consumers.
- Reducing the number of colchicine tablets prescribed or dispensed at one time.
- Use of child resistant packaging and blister packs.

Results: Sixteen fatal reports involving colchicine were identified in the CARM database. Of these, half involved individuals of Māori or

Pacific ethnicity, despite these groups representing about 25% of the population.

A total of 113 contacts have been made with the NZ Poisons centre in relation to patients exposed to colchicine, 32% of these were for intentional exposure.

Consumer information was produced and translated for relevant ethnic groups.

Changes to dispensing were rejected as these were considered to cause equity and adherence risks.

Reminders were provided to healthcare professionals via publications in *Prescriber Update* and through various Primary Care teaching and conference opportunities.

Conclusion: Reducing harm from colchicine in the community requires a cross-sector approach, and it is difficult to engage other organisations to take the lead. The medicines regulator may therefore need to coordinate and manage a project team in order to get buy-in and assistance from other stakeholders. Implementing changes for one particular safety concern can result in inadvertent new risks so it is important to get feedback from stakeholders to understand these issues.

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Analysis Of The Risk Of QT Prolongation In The Elderly Patients Undergoing Polypharmacy

Laura Costantino[1], Clizia Argirò[1], Francesca Saullo[2], Valentina Salerno[2], Rita Morrillo[2], Eugenia Daniele[2]

[1]University "Magna Graecia", Catanzaro, Italy. [2]University Hospital "Renato Dulbecco", Catanzaro, Italy

Introduction: Elderly patients are more exposed to drug toxicity due to reduced renal clearance, reduced hepatic metabolism and polypharmacy. The latter exposes the elderly patient to the risk of drug interactions that may lead to a QT interval prolongation. QT increase expresses a delay in the ventricular repolarisation phase and causes abnormal heartbeat. One of the main risks associated with it is the possibility of developing cardiac arrhythmias, even fatal ones such as torsades de pointes.

Aim/Objective: The aim of the study was to assess the risk of drug interactions that may cause long QT in a cohort of elderly patients admitted to the geriatrics ward of a hospital in southern Italy.

Methods: A team of pharmacists, in collaboration with physicians, consulted the medical records of 261 elderly patients on admission and 226 on discharge. The average age of the patients was 83.4 years and the observation period was from 08/01/2023 to 10/31/2023. From the medical records of each patient, it as possible to obtain the biographical data, pathologies, drug therapies carried out at home and medical prescriptions at discharge. The data were collected and processed using Excel®. The potential risks of polypharmacy were assessed by considering the drugs taken up to the time of admission, those prescribed at discharge and the change in this risk between the time of admission and discharge. Drug interactions were recorded using the clinical-management software InterCheck-WEB®.

Results: On arrival at hospital, 24.5% of patients were found to be on medication combinations that may lead to QT interval prolongation. At discharge, however, 29.2% of patients. The variation in risk between admission and discharge of patients is Δ +4.7%. The most commonly interacting drugs are those belonging to the group of proton pump inhibitors, diuretics, antipsychotics and antidepressants, as also shown in other studies [1, 2].

Conclusion: Our analysis shows that drugs that can prolong QT are widely prescribed in the elderly and particularly at the time of discharge. This suggests the need for a multidisciplinary team of physicians and pharmacists to carefully assess prescribing appropriateness in order to mitigate risks and ensure patient safety.

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Adverse Drug Reactions (ADRs) Associated with Anti-Tuberculosis Drugs: Retrospective Study

Bouraoui OUNI[1], Ferdaous CHAHED[1], Nesrine BEN SAYED[2], Raoudha SLIM[1], Raja GHEZEL[3], Malek SASSI[4], Ilyes TURKI[5], Neila FATHALLAH[1]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Hematology department, Farhat Hached hospital, Sousse, Tunisia. [3]Emergency department, Ibn Eljazzar Hospital, Kairouan, Tunisia. [4]Faculty of pharmacy, University of Monastir, Monastir, Tunisia. [5]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia

Introduction: Tuberculosis is one of the major causes of morbidity and mortality in the world. The minor side effects from the anti-tuberculosis drugs (anti-TB) are relatively common and manage by reassurance. However, the serious adverse events usually require discontinuation of all drugs. Because there are limited choices of second line antimycobacterium agents, some of the anti-TB drugs which may have caused initial adverse drug reaction (ADR) are occasionally needed to be reintroduced to the patients.

Aim/Objective: To assess the type and the frequency of ADR induced by anti-TB drugs reported to Regional Center of Pharmacovigilance of Sousse (Tunisia)

Methods: Collection of all ADRs induced by anti-TB drugs and reported to Regional Center of Pharmacovigilance of Sousse (Tunisia) during 10 years (from January 2014 to December 2023), All ADRs were identified and reviewed.

Results: We collected 85 patients treated with anti-TB drugs and presented ADRs during our study period. There was a clear predominance of women (69%), with a gender ratio of 0.45. The age ranged from 16 to 83 years old (mean 42.1). Only three patients with medical history of atopy. Diabetes and hypertension were the most common co-morbidity. All patients were given the combination form of Anti-TB drugs (HRZE). The average time to onset of events was 19.5 days. The most common ADR is liver injury in 61 patients (72%) (Hepatic cytolysis (N = 57), hepatic cholestasis (N = 2) and mixed disease (N = 2)). Other adverse events include 11 skin ADRs (13%), 07 (8 %) gastrointestinal ADRs (nausea/vomiting, abdominal pain, and diarrhea), 5 (6 %) neurological ADRs including 2 optic neuropathies.

Conclusion: Side effects to anti-TB drugs are common. Most of the minor ADRs can be controlled. Rechallenges and desensitization are possible. Minority of cases required discontinuation of all antimycobacterium in the regimen.

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Anti-tuberculosis Drugs (ATDs) Induced Hepatotoxicity

bouraoui OUNI[1], Ferdaous CHAHED[1], Neila FATHALLAH[1], Imen AKKARI[2], Awatef AZZEBI[3], Nesrine BEN SAYED[1], Ilyes TURKI[4]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Gastroenterology department, Farhat Hached hospital, Sousse, Tunisia. [3]Nephrology department, Sahloul hospital, Sousse, Tunisia. [4]Legal medicine department, Ibn Eljazzar Hospital, Kairouan, Tunisia

Introduction: Anti-tuberculosis drugs (ATDs), including isoniazid, rifampicin and pyrazinamide, are effective but sometimes induce liver toxicity in around 8% of patients (1), often leading to treatment discontinuation.
Aim/Objective: Describe the epidemiological and clinical features of liver damage associated with anti-tuberculosis drugs.
Methods: A retrospective descriptive study performed at the Regional Centre of Pharmacovigilance of Sousse over a period of 14 years (January 2006-December 2019). Causality relationship of liver injury and ATDs were done according to the method of Naranjo.
Results: A total of 74 patients were included in this study, predominantly women (N = 51); Sexe Ratio = 0.45. We observed 61 cases of liver damage (82.4%).
The mean age of the patients was 48.2 years [24-83 years].

The localisation of the tuberculosis was mainly lymph node (N = 44), pulmonary (N = 9), pleural (N = 4), digestive (N = 2) and urogenital (N = 2). The mean time to onset of hepatotoxicity was 40.8 days following treatment.

All patients received combined anti-tuberculosis treatment (HRZE).

Liver manifestations included hepatic cytolysis (N = 57), hepatic cholestasis (N = 2) and mixed disease (N = 2).

The most common grade of hepatic cytolysis was grade 2 (N = 26). Grades 1 and 3 accounted for 23 and 5 cases respectively, while the most severe grade 4 cases were less frequent (N = 3).

Pyrazinamide was the most frequently suspected of ATDs.

Treatment was discontinued in 38 patients with a favourable outcome, and continued under strict biological monitoring in the remaining cases with a favourable outcome.

Sequential reintroduction of ATDs in increasing doses was subsequently undertaken in 38 patients.
Conclusion: The study revealed a variety of liver injury induced by ATDs. Despite the seriousness of some cases, sequential reintroduction of ATDs with careful monitoring can reduce liver injury with ATDs.
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Priapism Induced by Sertraline: Case Report

bouraoui OUNI[1], Ferdaous CHAHED[1], Neila FATHALLAH[1], Med Ali KHALIFA[2], Malek SASSI[3], Nesrine BEN SAYED[4], Ilyes TURKI[5]

[1]Department of Pharmacology, Faculty of Medicine of Sousse, Sousse, Tunisia. [2]Orthopedic surgery department, Sahloul hospital, Sousse, Tunisia. [3]Faculty of pharmacy, University of Monastir, Monastir, Tunisia. [4]Department of Clinical Hematology , Farhat Hached Hospital, Sousse, Tunisia. [5]Legal medecine department, Ibn Eljazzar hospital, Kairouan, Tunisia

Introduction: Priapism, is a urological emergency disorder, is considered a rare medical condition characterized by a painful, persistent penile erection lasting more than 4 hours and occurring without any form of sexual stimulation. Antidepressants such as trazodone and phenelzine can induce priapism. However, priapism with selective serotonin reuptake inhibitors (SSRIs) seems to be a rare side effect.
Aim/Objective: We report a case of priapism probably induced by sertraline.
Methods: Not applicable.
Results: A 56-year-old man patient who was admitted to the emergency department due to prolonged painful erection. His past medical history included bipolar disorder since 20-year managed with lamotrigine, amitriptyline, and bromazepam. He had not experienced any sexual disorders under antipsychotics listed above. Sertraline was added to his medication regimen 3 months ago. According to the patient, erection had occurred spontaneously. There was no sexual stimulation and the patient denied any history of perineal or other penile trauma. He was not taking any drugs for erectile dysfunction and he denied illicit drugs intake, including cocaine and methamphetamine. In the emergency room, the patient was afebrile and hemodynamically stable. The patient's physical exam revealed painful penile erection with testicles pain. Laboratory tests including complete cell count were within normal limits. No evidence of disease can induce priapism such as multiple myeloma, sickle cell anemia, or thalassemia. In urological unit and under hemodynamic monitoring, the patient received normal saline irrigation in corpus cavernosum with 2 mg of phenylephrine instilled gradually with no decrease of rigidity. In front of poor response to medical treatment, the patient was brought to the operating room for caverno-spongiosal shunting. The surgical shunt was performed with no improvement of priapism. Therefore, drug-induced priapism was suspected and sertraline (the last drug introduced) was withdrawn and priapism was regressed progressively. The other medications were continued without incident.
Conclusion: Priapism is a rare but serious side effect of antipsychotics drugs including SSRI medications. Clinicians should be aware that the use of drug combinations with alpha-1 adrenergic receptor blocking propertie may increase the risk of priapism.
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Psychiatric decompensation after discontinuation of antiemetic neuroleptics

Amandine Calmettes[1], Jacques Hamard[2], Romain Barus[1], Claire De Canecaude[1], Pauline Schiro[1], wilhelm Storck[1], Francois Montastruc[1]

[1]University Hospital, Toulouse, Toulouse, France. [2]Gerard Marchant Hospital Center, Toulouse, France

Introduction: Psychiatric decompensations after discontinuation of antipsychotic neuroleptics may be interpreted as relapse of psychiatric illness or as an adverse drug reaction also identified as hypersensitivity psychosis.
Aim/Objective: In order to evaluate the risk of psychiatric decompensation after discontinuation of neuroleptics and to take into account indication bias, we performed a disproportionality analysis to investigate the risk of reporting psychiatric decompensation during withdrawal from neuroleptic antiemetics compared with withdrawal from setron antiemetics.
Methods: The study was based on data of Vigibase. Reports of antiemetics (neuroleptics and setrons) included in this study concerned adults over 18 years of age, of known sex, and registered between 1968 and January 30, 2023. Adverse events of interest ("cases") were reports coded with MedDRA terms as "drug withdrawal" in Standardised MedDRA Queries and "psychiatric conditions" defined from the System Organ Class level. This risk was estimated by calculating the reporting odds ratio (ROR) with 95% confidence intervals.
Results: In VigiBase, there were 75 754 reports with the antiemetic neuroleptics of interest, of which 54 cases were associated with psychiatric decompensation during withdrawal from these medications. Compared with the use of setron antiemetics, the use of neuroleptic antiemetics was associated with an increased risk of reporting psychiatric disorders during withdrawal (ROR 2.78 95% CI 1.52-5.09). The risk persisted when the analysis was restricted to neuroleptics with exclusively antiemetic iindication (ROR 2.22, 95% CI 1.18-4.18). Among the antiemetics, metoclopramide had the greatest risk of reporting (ROR 2.29, 95% CI 1.19-4.39).
Conclusion: This observational study suggests that withdrawal from neuroleptic antiemetics was associated with a greater risk of reporting psychiatric decompensation than withdrawal from setron antiemetics. Metoclopramide showed the highest risk, which is consistent with its greater propensity to cross the BBB compared with other neuroleptic antiemetics. This result supports the hypothesis of a risk of psychotic decompensation upon discontinuation of antipsychotic neuroleptics.
References

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Canadian Clinical Context: A Replicability and Validation Study of Naranjo Causality Assessment Tool

Pallavi Pradhan[1,2], Sonia Corbin[3,2], Shweta Todkar[2,3], Maude Lavallée[3,2], Isabelle Cloutier[3,4], Rosalie Darveau[4], Julie Méthot[2,3,4], Anick Bérard[5,6], Marie-Eve Piché[2,7], Jacinthe Leclerc[2,3]

[1]Departement of anatomy, University of Quebec at Trois-Rivieres, Trois-Rivieres, Canada. [2]Center of research, Institut universitaire de cardiologie et de pneumologie de Québec–Université Laval, Quebec, Canada. [3]Faculty of pharmacy, University Laval, Quebec, Canada. [4]Institut universitaire de cardiologie et de pneumologie de Québec–Université Laval, Quebec, Canada. [5]Research center of Ste-Justine university hospital center, Montreal, Canada. [6]Faculty of Pharmacy, University of Montreal, Montreal, Canada. [7]Faculty of Medicine, Université Laval, Quebec, Canada

Introduction: Patient safety has become a major concern in modern healthcare. [1] Research indicates that between 5-10% of patients experience an adverse event (AE) throughouttheir healthcare process, with a subset categorized as serious (SAE: resulting in hospitalisation or prolongation of existing hospitalisation, persistent or significant disability, birth defect, life-threatening or death). [2, 3] The causal assessment of SAE is the responsibility of healthcare professionals (HCP), who use their clinical judgment or a standardize tool in order to assess SAE. [4] Whether those two methods are comparable to provide similar results remains unclear.
Aim/Objective: To evaluate if the causality assessment performed by HCP is comparable using the 1981 Naranjo tool systematically, and to validate its performance whithin a Canadian clinical context.
Methods: A pilot retrospective cohort study was conducted, encompassing all patients with SAE admitted to the Institut universitaire de cardiologie et pneumologie de Québec–Université Laval in the year 2021. Twelve SAE were randomly selected for this pilot study. Electronic medical records were scrutinised to identify suspected drug products involved, with a causality assessment performed by HCP. Two reviewers independently assessed the 12 SAE for causality using the Naranjo tool. One had the expertise of working in the pharmacovigilance industry, while the other had experience working within the Canadian clinical setting as an HCP. Inter-rater reliability was assessed among the two reviewers and between HCP. Along with criterion validity (expert opinion was considered to be the gold standard), sensitivity and specificity was also calculated for validation study.
Results: The weighted kappa coefficient was 0.92, signifying good inter-rater reliability, with a kappa value of 0.84 indicating a good agreement between reviewers. No causality assessment by HCP were documented, rendering replicability computation impossible. The Naranjo tool showed positive monotonic correlation with expert opinion, resulting in $r_s = 0.208$ ($p < 0.001$). When categorizing Naranjo scores into binary variables, sensitivity was found to be 1.00, while specificity was 0.31.
Conclusion: Our study suggested that the Naranjo tool exhibits reliability and validity for application in clinical settings, successfully categorized all implicated drug products associated with SAE in our pilot investigation, however the low specificity of Naranjo tool may lead to many false negative. Larger scale studies need to be conducted in real-time clinical settings to investigate its performance and utility.
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An Audit on Adherence to Medicines and Healthcare Products Regulatory Agency Guidance to Reduce Risk in Rheumatoid Arthritis Patients on Janus Kinase Inhibitors

Ikra Ashraf, Amandeep Dhaliwal

Sandwell and West Birmingham NHS Trust, Birmingham, United Kingdom

Introduction: Janus Kinase Inhibitors (JAKi) are used to treat moderate to severe rheumatoid arthritis (RA). In April 2023, the MHRA (Medicines and Healthcare products Regulatory Agency) released guidance on risk minimisation measures for JAKi use in chronic inflammatory disorders [1].
This was following an observed increase in malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality in patients.

It was advised to avoid prescribing, unless there are no suitable alternatives, in patients with the following risk factors:

- Aged 65 years or older
- Current or past long-time smoking history
- Other risk factors for cardiovascular disease (CVD) or malignancy.

Aim/Objective: To identify which RA patients may be at an increased risk of adverse events, enabling risk-minimisation measures to be implemented.
Audit criteria were agreed based on the MHRA criteria listed above.
Methods: Eligible patients were identified retrospectively via a database and filtered according to the inclusion criteria.
Patients were analysed by accessing hospital notes and Rheumatology clinic letters from the past 12 months and checking for any risk factors documented. Compliance was documented for each patient using an anonymised spreadsheet and patient identifiers were stored on a single, secure document.
Results: Using the database, 175 patients were identified for inclusion.
It was found that, 31% of patients were aged 65 years or older, 17% were current or past long-time smokers, 9% had a past medical history of CVD, 3% had a history of malignancy and 3% had a history of VTE.

2 patients on a JAKi had three risk factors, 22 patients had two and 59 patients had one, that would predispose them to an increase in adverse effects.
Conclusion: The results illustrate that 48% of patients audited may require risk-minimisation measures initiated, or treatment suspended if alternatives are available. If patients must remain on a JAKi then, where applicable, they should be on a lower dose. This is only possible for Tofacitinib, Filgotinib and Baricitinib. For patients on Upadacitinib we would recommend switching to a JAKi that allows this.
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Overview of Causality Assessment of Adverse Events Among Drug Users in a Tertiary Hospital Setting: A Retrospective Study

Sonia Corbin[1,2], Maude Lavallée[1,2], Pallavi Pradhan[2,3], Magalie Thibault[2], Julie Méthot[1,2], Laura Blonde Guefack Djiokeng[3,2], Anick Bérard[4,5], Marie-Eve Piché[6,2], Fernanda Raphael Escobar Gimenes[7], Rosalie Darveau[2], Isabelle Cloutier[1,2], Jacinthe Leclerc[1,2]

[1]Faculty of Pharmacy, Laval University, Quebec, Canada. [2]Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, Quebec, Canada. [3]Anatomy Department, University of Quebec at Trois-Rivieres, Trois-Rivieres, Canada. [4]CHU Sainte-Justine Research Center, Montreal, Canada. [5]Faculty of Pharmacy, Montreal University, Montreal, Canada. [6]Faculty of Medicine, Laval University, Quebec, Canada. [7]Department of General and Specialized Nursing, University of São Paulo, Sao Paulo, Brazil

Introduction: Causality assessment determines the probability of a potential causal link between a drug and an adverse event (AE).(1) An AE is defined as any deleterious clinical manifestation that appears after medication use, without necessarily implying a causal link.(2) Causality assessment assists in obtaining a more accurate assessment of the risk/benefit ratio of a drug.(3, 4) Three methods are commonly used: 1) expert judgment, 2) algorithms and, 3) Bayesian or probabilistic approaches.(5, 6) More than 21 tools are available for causality assessment.(6) However, the proportion of AEs investigated for their causality remains poorly studied.
Aim/Objective: 1) Determine the proportion of AEs for which causality is investigated, 2) Inventory the causality assessment tools used by healthcare professionals.
Methods: We conducted a retrospective cohort study, including n = 500 (125 patients/year, between 2018 and 2021). The cohorts were randomized among all patients who were hospitalized in a tertiary care hospital in Quebec, Canada. Full episodes of care were examined using electronic medical records, from which relevant variables were extracted: 1) demographic, 2) hospitalization, 3) drug product, 4) AE and, 5) causality assessment. Descriptive analysis (median, minimum-maximum, proportion) was conducted to characterize the population sample and address our objectives.
Results: The characteristics of all patients randomized to the study were as follows: median age, 69 years old (range: 21-96 yrs), 43.6% women, median comorbidities/patient 4 (1-12). In total, 2541 AEs, including 302 SAEs (8.4%), were listed in our sample, corresponding to a median of 4 (0-40) AEs/patient. The main AE class was cardiac disorders. A total of 9568 drug products were taken by the cohorts, with a median of 18 (2-56) per patient. Among them, 76 were suspected of causing AEs. Among all AEs (n = 2541), the process of causality assessment was never documented in the medical records (n = 0, 0%). Thus, no causality assessment tool could be identified (n = 0,0%).
Conclusion: Reporting of drug-associated AEs, including causality assessment, facilitates earlier identification, reporting, and management of drug safety signals. However, there are currently no guidelines for proper causality assessment, and no causality assessment tool is universally accepted.(5, 6) We report that no AEs were documented for causality in this pilot study. Therefore, the introduction of guidelines on causality assessment would be an interesting avenue to improve drug safety for the population.
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Paternal Exposure to Medicines Leading to Detrimental Outcomes in Offspring: A Scoping Review

Daniel Malek, PharmD, MSc[1,2], Yulia Vasianovich, PhD, RAC[2], Flavia Stana, PharmD, MSc[2], Eva-Marie Neumann, MLIS[2], Marc F. Poitras, MSc, PhD, MBA[2], Mohammed T. Ansari, MD, MMedSc, MPhil[2]

[1]Université de Montréal, Montréal, Canada. [2]Santé Canada/Health Canada, Ottawa, Canada

Introduction: Valproate is an anti-epileptic drug that has been on the market for several decades. The association between maternal valproate exposure in pregnancy and adverse offspring outcomes has been well established. Consequently, various risk minimisation measures have been implemented globally to mitigate these safety concerns. Similar precautions have been taken with numerous other medicines, for which harmful mechanisms of action and specific at-risk trimesters have been elucidated. While the study of detrimental offspring outcomes induced through maternal exposure has advanced significantly in the past decades, limited knowledge exists about the effects of paternal exposure.

Aim/Objective: This scoping review aimed to explore and chart the published scientific literature reporting on the occurrence of detrimental effects in offspring following paternal exposure to medicines that are not established to pose a risk on the subsequent generations. The objective was to identify knowledge gaps and guide future research on the topic.

Methods: Embase, MEDLINE, Global Health, and APA PsycInfo were searched from the database inception date to January 27, 2024. Citations were uploaded to Covidence and were screened based on their titles and abstracts, then by their full texts. Included citations were extracted and charted to address the following questions:

- Which classes of medicines were mostly studied and reported to be linked to detrimental outcomes in offspring following paternal exposure?
- What were the outcomes assessed in offspring?
- What timing of paternal exposure was investigated?
- What study designs were used to study paternal exposure and the association with detrimental outcomes in offspring?

Results: The literature search yielded 966 human study articles, 62 systematic reviews/meta-analyses and 362 animal/in vitro study articles. After screening and focusing only on human studies, 32 primary articles and 4 systematic reviews/meta-analyses were included in the analysis. The majority of studies focused on adverse offspring outcomes associated with paternal exposure to immunosuppressants and antineoplastic agents, primarily investigating congenital malformations (CM), preterm births (PTB), and small for gestational age (SGA) outcomes during the preconception period. Scandinavian studies with large sample sizes contributed significant insights, particularly in medicines affecting the nervous system.

Conclusion: Our study underscores the critical need for further research utilising robust comparative methodologies to elucidate the clinical implications of paternal medication exposure on adverse offspring outcomes. Leveraging experiences from Scandinavian countries in large-scale prospective research will be essential in informing evidence-based practices and regulatory decisions in pharmacovigilance.

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Genome-Wide Association Study of Direct Oral Anticoagulants and Their Relation to Bleeding

Sofia Attelind[1,2], Niclas Eriksson[3], Mia Wadelius[1], Pär Hallberg[1]

[1]Department of Medical Sciences, Clinical Pharmacogenomics, Uppsala University, Uppsala, Sweden. [2]Department of Drug Safety, Swedish Medical Products Agency, Uppsala, Sweden. [3]Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala, Sweden

Introduction: Direct oral anticoagulants (DOACs) are used for the prevention and treatment of thromboembolic events [1]. Studies indicate the potential of pharmacogenomics to help explain the interindividual variations in the occurrence of adverse drug reactions (ADRs) to DOACs [2].

Aim/Objective: The aim was to investigate whether there is a genetic predisposition to bleeding during DOAC therapy.

Methods: Within the Swedegene project [3], we conducted a genome-wide association study (GWAS) of bleeding during DOAC therapy. Cases were recruited from spontaneous ADR reports sent from health-care professionals to the Swedish Medical Products Agency. All reports of a bleeding event associated with DOAC treatment in adults received up until May 2021 were retrieved. Events were categorised as major, minor, or clinically relevant non major bleeding (CRNM) and each case was adjudicated by two specialists. A total of 4891 unrelated individuals from the Swedish TwinGene biobank were used as population controls. A subgroup matched for DOAC exposure was also used (n = 353).

Pre-specified candidate gene and single nucleotide polymorphism (SNP) analyses were performed separating dabigatran (direct thrombin inhibitor) from the other DOACs (factor Xa inhibitors).

The genome-wide analyses were performed using SAIGE (Scalable and Accurate Implementation of GEneralized mixed model [4]). All genome-wide analyses were adjusted for sex and the first six principal components. This study was approved by the Swedish Ethical Review Authority (2010/231, Uppsala).

Results: In total 130 cases of bleeding (60% men) were recruited and were categorised as major (n = 45), minor (n = 37), or CRNM (n = 48). Most individuals received factor Xa inhibitors (apixaban, rivaroxaban or edoxaban), while 15 cases received the direct thrombin inhibitor dabigatran. Most, 93%, were of Swedish ancestry, 6% of other European ancestry, and the remaining 1% of other ancestry.

In the gene set analysis, coding variants in *ABL1* were significantly associated with major and CRNM bleeding, $P = 1.94 \times 10^{-6}$. The top *ABL1* SNP was rs2229067C>T, OR 4.32, P = 0.000161.

In the candidate gene analysis of factor Xa inhibitors, rare coding variants in *VWF* were significantly associated with bleeding, P = 0.00171, and with major and CRNM bleeding, P = 0.00208.

No genetic marker passed the significance threshold in the full GWAS analysis. When cases were compared with controls matched for DOAC treatment, *BAIAP2L2* rs142001534 passed the significance threshold, $P = 4.66 \times 10^{-8}$.

Conclusion: The results of this study suggest that rare variants in the von Willebrand factor gene *VWF* may be associated with bleeding in patients treated with factor Xa inhibitors. Certain variants of VWF are

known to cause a hereditary bleeding disorder [5]. Other findings are less straightforward and should be interpreted with caution.

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Sacubitril-Valsartan and Risk of Alzheimer-Type Dementia: A Disproportionality Analysis

Atefeh Jafari[1], Niaz Chalabianloo[2], Flory Tsobo Muanda[1,2,3,4]

[1]Department of Epidemiology & Biostatistics, Western University, London, Canada. [2]Department of Physiology and Pharmacology, Western University, London, Canada. [3]Lawson Health Research Institute, London Health Sciences Centre, London, Canada. [4]ICES Western, London, Canada

Introduction: Neprilysin, a crucial enzyme for clearing Amyloid-β content associated with Alzheimer's disease, is inhibited by sacubitril in Sacubitril-valsartan.[1-3] While effective in treating chronic heart failure, concerns remain about Sacubitril-valsartan's long-term effects on cognitive function. Using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, we conducted a disproportionality analysis to quantify the risk of Alzheimer 's-type dementia associated with Sacubitril-valsartan.

Aim/Objective: To examine whether Sacubitril-valsartan is associated with a higher risk of Alzheimer 's-type dementia than other medications.

Methods: We analyzed adverse drug events (ADEs) reported to FAERS databases from 2015Q3 to 2023Q3 using Open vigil 2.1-Medical Dictionary for Regulatory Activities (MedDRA)-v24. The outcome of interest was Alzheimer-type dementia identified using the following MedDRA preferred terms: 'dementia Alzheimer's type,' dementia of the Alzheimer's type, uncomplicated,' 'dementia of the Alzheimer's type, with delirium,' ' dementia of the Alzheimer's type, with delusions.' The study drugs were Sacubitril-valsartan and other drugs. Reporting odds ratios (ROR) were used to compare the proportion of Alzheimer-type dementia reports for Sacubitril-valsartan compared to those for other drugs to detect potential signals. We also repeated the primary analysis with lisinopril and losartan, which served as active comparator groups. All analyses were restricted to ADEs considered the primary suspects in the database.

Results: Our study showed that Sacubitril-valsartan (155 cases of 102,968 [0.15%] vs. 2,571 cases of 8,024,146 [0.03%]; ROR, 4.7 [95% CI, 3.99 to 5.53]) had a higher proportion of Alzheimer-type dementia reports than other medications. No signal was observed for lisinopril or losartan.

Conclusion: Sacubitril-valsartan may be associated with a higher risk of Alzheimer-type dementia. Further pharmacoepidemiologic studies are needed to confirm these findings.

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A Patient Safety Competency Model for Measuring and Building Pharmacovigilance Skills in a Developing Organization

Karen Schmidt, Faizan Mujeebuddin, Danielle Abatemarco

BeiGene USA, Inc., Ridgefield Park, NJ, USA

Introduction: BeiGene's rapidly maturing and expanding Global Patient Safety (GPS) department necessitated a systematic view of our workforce's competency needs. A comprehensive Competency Model of Pharmacovigilance (PV)-specific knowledge and skills was developed that incorporates six essential PV-specific competency areas of expertise: PV Scientific, PV Digital, PV Operational, PV Regulatory, PV Product Role, PV Organizational Role. The model incorporates the mission and purpose of global PV functions with the need to optimize and develop our pharmacovigilance workforce.

Aim/Objective: Develop a comprehensive model of skills and knowledge required to support Global Patient Safety functions in a pharmaceutical company.

Methods: A catalogue of specific knowledge and skills required by pharmacovigilance roles was compiled from industry documents as well as job descriptions within GPS. Through a consensus process, six categories of PV competency were described. The PV Competencies were validated in focus groups with pharmacovigilance experts. The competency model developed includes proficiency levels that reflect the growth of knowledge and skill throughout a career in Patient Safety.

Results: The Competency Model includes six patient safety competencies: PV Digital Expertise, PV Regulatory Expertise, PV Scientific Expertise, PV Operational Expertise, PV Product Role, and PV Organizational Role. We refined our model, adding six developmental stage descriptions for each of the six patient safety competency categories. In Stage 0, the competency is "not present". In Stage 1 "Developing", colleagues have some experience, skill, or knowledge of this competency but they are not regularly deploying their knowledge. In Stages 2 "Supporting" through 4 "Leading", the expectation is that the employee is displaying this competency in everyday tasks for their role. Stage 5 "Shaping" was reserved for employees who have a high degree of the relevant skills and abilities for the competency and are thus capable of shaping the design of systems and policies governing the deployment of the competency.

Conclusion: Based on our experience developing and validating the Patient Safety Competency model, the development of the PV workforce is poised to benefit at all points from a foundation based on competencies. For supporting individual employees and roles, the Competency Model will form the basis of our Learning and Development Program, Individual Development Plans, Performance Evaluation, and Succession Planning. Considering the Patient Safety work force in the aggregate, an understanding of the sum of competencies across our department will be used to inform project

resourcing and planning for activities that are cross-functional and reach beyond individual role-based duties and tasks.

References

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A Proprietary Solution for Resource Management in Safety Organizations, Centered around Individual and Organization Skillsets

Avani Shah[1], Danielle Abatemarco[1], Koleen Steiner[2], Jason Miller[2], Rajat Gupta[3]

[1]BeiGene USA, INC, Ridgefield Park, USA. [2]BeiGene USA, INC, Menlo Park, USA. [3]BeiGene USA, INC, Emeryville, USA

Introduction: Maintaining a dynamic yet sustainable workforce during global expansion is challenging. Rapidly scaling a patient safety organization requires proper utilization and retention of resources, leveraging diverse and specialized skillsets, to execute and drive performance.

Aim/Objective: To design and implement a fit-for-purpose resource management solution comprised of a framework, process and data visualization tools.

Methods: A prospective study of initiatives with existing talent pool was initiated, categorizing resources by skillset to establish efficient utilization across the organization. Genericized roles were crafted within the resource management solution, for which identification of key resources and skills would be utilized across patient safety's portfolio of work. Initiatives were categorized into distinct "project types" and codified against these to produce baseline resourcing needs for forecasting planned and unplanned activities (Fig. 1). Upcoming internal audits and inspection efforts were treated as a project type to ensure adequate resource availability towards these core activities. A framework for ongoing resource management and a structured approach to quantitative decision-making was designed, implementing monthly review meetings in which discussions around resource utilization efficiency, quantitative forecasting and project prioritization may be had using data.

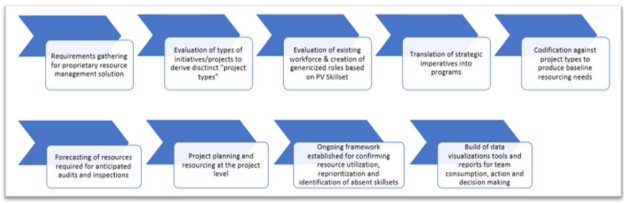

Figure 1. The process of designing and building a proprietary resource management platform for use in PV organizations.

Results: The resource management solution was implemented for 100% of safety's known project efforts (N = 28). The tool is comprised of 50 people tags based on ISOP's PV Competency framework[1], which were created to differentiate subject matter expertise across the talent pool. Thirteen (13) project-level roles and seven (7) project types were determined. Project types each contain a baseline set of required roles, their time allocation and project duration. Accompanying the dynamic digital dashboard, 4 live reports were configured to provide present and future resource availability to pinpoint staffing gaps, over-allocation and under-utilization of resources across our safety organization.

Conclusion: The resource management solution enables data-driven decision making for directing resources towards impactful business initiatives based on that individual's skillset and remit. The solution provides data for leadership to identify areas of efficiency in driving better utilization of internal resources, identifying the need for external support, and identifying persistent business needs in the future that may be addressed by upskilling the existing workforce. Over time, the resource management solution will capture the variance between anticipated and actual resource allocation, providing insights into individuals who are over- or under-utilized in driving for better distribution of work, and ultimately work/life balance, across the organization.

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Enhancing Safety: A Proof-of-Concept Pilot Study to Establish a Framework for Pan-Canadian 2SLGBTQI+ Medication Safety Initiatives

Payam Peymani[1,2], Sean Irvine Irvine[2]

[1]Children's Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg, Canada. [2]Pride Winnipeg, Winnipeg, Canada

Introduction: Sexual and Gender Minority (2SLGBTQI+) individuals face unique health disparities, with limited research on adverse drug reactions (ADRs). This knowledge gap hinders optimal healthcare and disproportionately impacts this vulnerable population.

This pilot study is crucial for establishing a framework for larger, Pan-Canadian initiatives focused on 2SLGBTQI+ medication safety. By addressing Equity, Diversity, and Inclusion (EDI) in research design and accessibility, this project aims to generate generalizable knowledge applicable across Canada.

Aim/Objective: We explore potential risk factors for medication-related issues among 2SLGBTQI+ individuals in Manitoba, leveraging partnerships with Pride Winnipeg and The Manitoba Pride Alliance.

Methods: This pilot study employs a retrospective observational design (utilizing existing data and self-reported experiences) to explore potential risk factors for medication-related issues among 2SLGBTQI+ individuals in Manitoba. Data will be collected through collaborations with organizations like Pride Winnipeg and healthcare providers specializing in 2SLGBTQI+ care. Accessible methods will be prioritized, including existing anonymized datasets, online/paper surveys, and optional semi-structured interviews. The collected data will be de-identified and analyzed to identify associations between medication classes and medication-related issues. Additionally, demographic factors influencing issue severity will be explored. This pilot project establishes a framework for future, large-scale studies with national impact.

Results: This initial phase will:

- Identify potential associations between medication classes and medication-related issues in the 2SLGBTQI+ community.
- Explore demographic factors influencing the severity of medication-related issues (age, gender identity, socioeconomic status).
- Develop a framework for future, large-scale studies with national impact.

Conclusion: This pilot project lays the groundwork for pan-Canadian research on 2SLGBTQI+ medication safety. By prioritizing accessibility and EDI, the findings will inform culturally competent guidelines to improve medication experiences for 2SLGBTQI+ individuals across Canada.

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Perspectives and Challenges of Marketing Authorisation Holders in Implementing a Pregnancy Prevention Programme (PPP) in Singapore

Aileen Chua, Michael Limenta, Xue Zhen Leng, Zhang Ting Ong, Pui Ling Lee, Phey Yen Han, Jalene Poh

Vigilance & Compliance Branch, Health Products Regulation Group, Health Sciences Authority, Singapore, Singapore

Introduction: Determination of the effectiveness of Pregnancy Prevention Programmes (PPP) has traditionally relied on pregnancy exposure outcomes to assess the need for additional risk minimisation measures (i.e. "PPP-related activities"). However, a stringent PPP may not significantly reduce pregnancy rates during treatment [1, 2] and there remains a lack of understanding regarding the challenges encountered by Marketing Authorisation Holders (MAHs) in designing and implementing an optimal PPP. A review of the PPP processes, including the challenges faced by MAHs, could enhance compliance and improve the effectiveness of a PPP.
Aim/Objective: As part of the local PPP framework review, we conducted a survey to understand the perspectives and practical challenges encountered by MAHs in implementing PPP-related activities for their products in Singapore.
Methods: An online survey was conducted among all MAHs of products with PPP-related activities, namely oral retinoids and thalidomide and its analogues (isotretinoin, acitretin, thalidomide, lenalidomide, pomalidomide). The survey was designed to gather insights on the current activities implemented locally and the challenges encountered during their implementation, feedback received by the MAHs from local healthcare professionals (HCPs), and MAHs' views on the critical components to be included in a local PPP.
Results: Responses were received from 7 of the 9 MAHs (78%). Administrative challenges, specifically obtaining signed letters of undertaking and providing educational materials to HCPs, were encountered by 57% of the respondents due to uncertainties in process requirements and changes in HCPs' place of practice. Difficulties with ensuring HCPs' compliance with company-introduced process, such as training and completion of forms, were also reported by 29% of the respondents, which were attributed to the HCPs' heavy workloads. Furthermore, 29% of the respondents highlighted a lack of visibility and control over PPP processes carried out in healthcare institutions and across the distribution chain. Four MAHs expressed consensus on the need to streamline processes and emphasised the shared responsibilities with HCPs in ensuring the effective implementation of a PPP.
Conclusion: The survey results highlighted the challenges with administrative issues, HCP engagement, and control and oversight of the PPP faced by MAHs in implementing a PPP and underscore the importance of considering HCPs' perspectives in its design. The subsequent phase of this initiative will involve engaging HCPs to gather their views on PPP criteria and requirements. The insights gathered will aid in strengthening the PPP framework in Singapore.
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Looking to the Future: Disproportionality Analysis Provides Critical Insights into CAR T-Cell Safety and Secondary Malignancy Risk (FAERS Pharmacovigilance Database)

Raffaella Di Napoli, Nunzia Balzano, Consiglia Riccardi, Annamaria Mascolo, Annalisa Capuano

Department of Experimental Medicine, Section of Pharmacology "L. Donatelli", University of Campania "Luigi Vanvitelli", Napoli, Italy

Introduction: One of the most revolutionary immune-targeted therapies is chimeric antigen receptor (CAR) T-cell therapy, which has shown remarkable efficacy in the treatment of several types of haematological tumours. On 28 November 2020, the FDA highlighted safety concerns regarding the development of T-cell malignancies in some patients following CAR T-cell therapy [1, 2].
Aim/Objective: This pharmacovigilance study aims to determine the reported probabilty of T-cell malignancies, particularly T-cell lymphoma, following CAR T-cell therapy.
Methods: Individual case safety reports (ICSRs) reporting at least one CAR T-cell therapy as a suspect drug were extracted from the Food and Drug Administration Adverse Event Reporting System database, up to 6 February 2024. Descriptive and disproportionality analyses were performed.
Results: T-cell malignancies were described as adverse events in a total of 17 out of 11,786 ICSRs reporting a CAR T-cell therapy as suspected drug. Five ICSRs were referred to axicabtagene ciloleucel, 4 to ciltacabtagene autoleucel, 1 to lisocabtagene maraleucel, and 7 to tisagenlecleuce. Overall, the gender distribution was nearly equal between females and males (N = 8; 47.1% and N = 7; 41.2%, respectively) and adult patients accounted for 41.2% of ICSRs (N = 7). All cases were classified as serious and the 41.2% (N = 7) had a fatal outcome. The most frequent PTs indicative of T-cell malignancies was "T-cell lymphoma" (N = 12; 70.6%), followed by "Peripheral T-cell lymphoma unspecified" (N = 3; 17.6%), "angioimmunoblastic T-cell lymphoma" and "enteropathy-associated T-cell lymphoma" (N = 1; 5.9%, both). Looking at the type of all other events, the highest percentage belonged to the System Organ Classes "Gastrointestinal disorders" [14.3%, with "Gastrointestinal motility and defaecation conditions" as the first represented High-Level-Group- Terms (N = 4; 30.8%)].
Axicabtagene ciloleucel and tisagenlecleucel were associated with a higher reporting probability of T-cell lymphoma compared to all other drugs (ROR 21.19; 95 % CI 7.93-56.59 and ROR 57.20; 95 % CI 25.61-127.74, respectively). A higher reporting probability of T-cell lymphoma was also found when tisagenlecleucel was compared with axicabtagene ciloleucel (ROR 2.69; 95 % CI 0.76-9.55,).
Conclusion: The disproportionality analysis suggests that both axicabtagene ciloleucel and tisagenlecleucel may be associated with a higher risk of T-cell lymphoma than other drugs. In addition, axicabtagene ciloleucel was associated with a higher frequency of T-cell lymphoma reports compared to tisagenlecleucel.
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Neurological and Neuropsychiatric Adverse Drug Reactions to Integrase Strand Transfer Inhibitors: 10-Year Review of Reports to the European Pharmacovigilance System

Pedro Benjamim[1], Joao P. Fernandes[2], Paula Moreira[3], Isabel Silva[3], Márcia Silva[4]

[1]Santa Maria Local Health Unit, Lisbon, Portugal. [2]Directorate for Risk Management of Medicines, INFARMED - National Authority of Medicines and Health Products, I.P, Lisbon, Portugal., Lisbon, Portugal. [3]São João Local Health Unit, Porto, Portugal. [4]Directorate for Risk Management of Medicines, INFARMED - National Authority of Medicines and Health Products, Lisbon, Portugal

Introduction: Integrase strand transfer inhibitors (INSTIs) are considered first-line therapies for treatment-naïve Human Immunodeficiency Virus (HIV)-infected patients and are generally well tolerated, exhibiting good efficacy and fewer drug interactions compared to other antiretroviral drug classes. Despite their efficacy, there is growing recognition of multifaceted nature of adverse drug reactions (ADRs) linked to these medicinal products. The onset of neurological and neuropsychiatric symptoms, particularly when severe, may prompt the suspension or modification of therapeutic interventions. It's crucial to raise awareness of this issue, highlighting the importance of recognizing and addressing neurological and neuropsychiatric manifestations during the course of treatment.
Aim/Objective: This study aims to assess Individual Case Safety Reports (ICSRs) associated with INSTIs reported to the European Pharmacovigilance System, focusing on ADRs, particularly neurologic and neuropsychiatric symptoms.
Methods: We conducted a retrospective analysis of ICSRs containing at least one medicinal product under the ATC code J05AJ (Integrase Inhibitors) reported as suspect/interacting to the EudraVigilance database, from January 1, 2014, to December 31, 2023, in a post-marketing context. Clinical judgement was employed to assess ICSRs and identify MedDRA Preferred Terms (PT) related to neurological and neuropsychiatric symptoms.
Results: Our research retrieved a total of 13255 ICSRS, with the majority relating to dolutegravir. A wide array of neurologic ADRs associated with the use of INSTIs, was detected. Peripheral neuropathy was one of some notable neurological symptoms, potentially impacting therapy adherence and requiring treatment discontinuation. Additionally, a complex interplay between psychiatric and neurological symptoms was also observed, highlighting the need for heightened clinician awareness during prescription and monitoring.
Conclusion: Our study underscores the multifaceted nature of ADRs, particularly neurologic and neuropsychiatric adverse reactions, linked to INSTIs. These findings emphasize the importance of comprehensive assessment and tailored management strategies to optimize treatment outcomes and patient well-being, thus accentuating the crucial role of effective management in enhancing treatment adherence and overall therapeutic success. Further research is warranted to deepen our understanding of these ADRs and refine therapeutic approaches in HIV care.

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Training Programs to Develop a Pool of DSMB Members from LMICs and Training for LMIC Vaccine Clinical Trial Investigators

Steven Black[1,2], Esperança Sevene[3], Cornelia Dekker[4], Catherine Tencza[5], Alex Dodoo[6], Miriam Sturkenboom[7], Robert Chen[2]

[1]Global Vaccine Data Network, Auckland, New Zealand. [2]Brighton Collaboration, Atlanta, USA. [3]Eduardo Mondlane University, Maputo, Mozambique. [4]Stanford University, Palo Alto, USA. [5]Tencza Designs, Atlanta, USA. [6]Ghana Standards Authority, Accra, Ghana. [7]Utrecht University, Utrecht, Netherlands

Introduction: Clinical trials conducted to evaluate the new vaccines and other medical interventions benefit from independent Data Safety Monitoring Boards (DSMBs). DSMBs help provide critical oversight over safety, efficacy, and decision making based on trial data, but historically lacked formal training and expertise in vaccine safety (including epidemiology of rare events).
Aim/Objective: The Coalition for Epidemic Preparedness Innovations (CEPI) and others are sponsoring development of vaccines that will be tested and used almost exclusively in LMICs. Examples include vaccines for malaria, Lassa Fever, Rift Valley Fever, MERS, and Nipah virus. Local involvement and expertise are critical to maintain the credibility of the process. However, there is a shortage of individuals with DSMB experience from LMICs. To address this need, CEPI funded the Safety Platform for Emergency vACcines (SPEAC) project to develop an eight-week training program for prospective DSMB members. In addition, because CEPI is funding clinical trials to evaluate Lassa Fever vaccines in West Africa, the original DSMB training program was adapted to train investigators in evaluation of safety and efficacy during vaccine clinical trials.
Methods: The DSMB training program contains weekly online modules on different topics along with a live session to discuss the material and answer questions (Table shows the main topics covered.) There are weekly quizzes and a final exam. When these are completed, a certificate is issued.

TABLE: DSMB Training Course Program

Week	Module
1	Overview of the training, importance of the DSMB
2	Good Clinical Practice, differences between assessment of drug and vaccine safety
3	Vaccine Clinical Trials; responsibilities, statistical considerations
4	Role of the DSMB, causality assessment, immunologic assessment
5	Reviewing a protocol, epidemiology of rare events
6	Regulatory considerations for organizing a DSMB, developer requirements
7	DSMB Meetings: Safety review, decision making considerations
8	Conclusion: review of the course, course takeaways, course final exam

Results: Four DSMB and one investigator trainings have been conducted to date with about 15 participants in each course. Post-training surveys indicated that participants almost uniformly thought that the course was highly valuable and relevant to their work, with review scores of 4.9 out of five or higher. A pool of 60 trained persons is now available for developers who seek local expertise for DSMBs in LMICs.
Conclusion: Formal training for DSMB participants and ensuring this includes developing expertise in assessing safety will help ensure improved oversight of future clinical trials in LMIC.

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Annual Report of Adverse Reactions Associated with Cannabis Products Reported to Health Canada, 2022

Sieara Plebon-Huff, Safia Hassan, Nadia Aziz, Marko Cavar, Maria Aoun, Shahid Perwaiz, Hanan Abramovici

Health Canada, Ottawa, Canada

Introduction: Health Canada's Vigilance Framework for Cannabis Products allows for the detection, collection, monitoring, and assessment of adverse reaction reports to support decision-making, knowledge translation and communication of the risks of cannabis products to the public. With the rising prevalence of cannabis consumption in Canada and a constantly expanding cannabis product marketplace, it's important to continue to monitor any potential adverse reactions arising from the use of cannabis and cannabis products particularly given that consumers have differing risk profiles that may increase the potential risk of experiencing adverse reactions to cannabis.
Aim/Objective: To summarize adverse reaction reports associated with legal cannabis products reported to Health Canada during the 2022 calendar year.
Methods: Adverse reaction reports are submitted to Health Canada by consumers and health professionals on a voluntary basis, and by licence holders who are obligated to report serious adverse reactions per the *Cannabis Regulations*. Reports are received and coded in the Canada Vigilance Database by the Marketed Health Products Directorate within the Health Products and Food Branch. The Office of Cannabis Science and Surveillance within the Controlled Substances and Cannabis Branch is responsible for the detection, monitoring, prioritization, and evaluation of cannabis adverse reactions, as well as the development and implementation of associated risk mitigation strategies where necessary.
A descriptive analysis of all cases involving legal cannabis products in a suspected role and received from January 1, 2022 to December 31, 2022 was conducted to better understand case patterns by demographic and use characteristics during the reporting period.
Results: A total of 92 adverse reaction cases involving legal cannabis products were reported to Health Canada in 2022. Most cases involved males (40%), cannabis use for self-reported medical purposes (51%) and cannabis extracts (53%). The most frequently reported medical event was hallucination. Of the events assessed, most were assigned a causality of 'Possible' meaning the product may have contributed to the adverse reaction, but the contribution of other factors cannot be ruled out.
Conclusion: Health Canada continues to publish public-facing surveillance reports of cannabis adverse reactions on an annual basis and uses these data to inform educational and outreach resources for consumers, healthcare professionals and other reporters. These data may also inform other risk mitigation activities, such as risk communications.
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Enhancing Patient Safety with Dashboard for Advanced Safety Analytics Exploration: A Step Towards Proactive, Personalized, and Predictive Drug Safety Management

Yingjia Chen[1], Seid Hamzic[2], Svetlana Lyalina[1], Chu-Fang Lin[1], Martin Schaerer[2], Robert Walls[2]

[1]*Genentech, South San Francisco, USA.* [2]*Roche, Basel, Switzerland*

Introduction: The Dashboard for Advanced Safety Analytics Exploration (DASAE) project seeks to innovate in drug safety signals detection, risk management and causality assessments for pharmaceutical products. It leverages data from clinical trials, real-world data (RWD) from the Flatiron Health electronic health record (EHR)-derived de-identified database, spontaneous reporting databases and academic literature, aiming to enhance safety quantitative research and optimization of decision-making for patient benefit through the integration of two core components: analytical solutions and AI-enabled tools.
Aim/Objective: Our goal is to enhance quantitative safety research and improve decision-making for patient benefit by harnessing a synergistic platform of analytical solutions and AI-enabled tools.
Methods: The project encompasses:

- Analytical solutions: 1) Concurrent depiction and visualization of patient populations across multiple data sources, including clinical trials, RWD, and spontaneous reporting databases; 2) Comparative analyses of incidence risk/rate from diverse data sources using; 3) Generation of causal hypotheses, including identification/quantification of mediators and moderators; 5) Comprehensive meta-analysis combining internal analyses with existing research; 6) Predictions at the patient level and projections at the population level regarding safety risks, including event timing.
- AI-enabled tools: Exploration of large-language models (LLMs) to assist in three domains: 1) Creation of causal hypotheses and identification of risk factors; 2) Literature review and classification of publications to support meta-analysis; 3) Transformation of complex clinical patient narratives into structured, tabulated data.

Results: Prototypes for LLM -assisted causality assessment and literature review are completed. A platform encompassing all functionalities is in development. A pilot study is underway, with comparative analysis completed and other features being developed.
Conclusion: DASAE exemplifies a proactive, personalized, and predictive approach in pharmaceutical safety, anticipating significant cost savings and optimization decision-support for patients. We aim to explore its full potential in enhancing operational efficiency, facilitating personalized risk management, and supporting evidence-based health authority interactions. This project marks a significant stride in integrating advanced technology and analytics in pharmaceutical safety, aligning with evolving enterprise priorities.
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Risk Factor Identification for Anemia and Immune-Related Hepatitis in NSCLC Patients Treated with PDL1/PD1: Single-Source vs Meta-analysis Coefficient Estimates

Svetlana Lyalina[1], Chu-Fang Lin[1], Monika Kaul[1], Seid Hamzic[2], Martin Schaerer[2], Robert Walls[3], Yingjia Chen[1]

[1]*Genentech, South San Francisco, USA.* [2]*Roche, Basel, Switzerland.* [3]*Roche, Basel, Swaziland*

Introduction: Identifying risk factors in drug development is vital for patient safety and anticipating adverse reactions. Traditional qualitative analyses, though valuable, are limited in scope and often overlook critical risks by not fully representing diverse populations. This can result in biased findings and miss rare risks, underscoring the need for broader, more powerful analytical methods in risk assessment.
Aim/Objective: The aim of this study is to compare the effectiveness of risk factor identification from a single-source dataset (clinical trial, RWD, and spontaneous reporting database) versus meta-analysis in

contextualization of anemia and immune-related hepatitis in NSCLC patients treated with PD-L1/PD-1 inhibitors.

Methods: This retrospective, secondary data use observational study assessed and compared risk factors of anemia and immune-mediated hepatitis in Stage IIIb/IV NSCLC patients treated with PD-1/PD-L1 drugs. Data from the TAIL study (NCT03285763), the nationwide, electronic health record-derived, de-identified Flatiron Health (FH) NSCLC database, and the Roche ARISg database (up to August 31, 2023) were analyzed. MICE/missRanger handled missing data imputation, with Out-Of-Bag mean prediction error indicating imputation performance. Individual logistic regression was used to identify risk factors from each single data source. Additionally, a 2-step meta-analysis and meta-analysis using Generalized Linear Mixed Models (GLMM) were developed for comparative purposes. This comprehensive analytical approach allowed for: 1) the identification and comparison of risk factors sets across different data sources, 2) the examination of the magnitude of identified risk factors, and 3) the quantification of uncertainties surrounding these risk factors.

Results: Analyzing anemia across datasets finds significant risk factors: the TAIL dataset highlights White race (OR: 0.21 [0.09, 0.50]) and baseline hemoglobin (OR: 0.69 [0.58, 0.82]). Flatiron Health (FH) shows age (OR: 0.94 [0.90, 0.97]) as a factor, while ARISg indicates "other" race (OR: 0.26 [0.08, 0.85]) and previous radiotherapy (OR: 6.70 [2.19, 20.54]). GLMM meta-analysis confirms baseline hemoglobin (OR: 0.85 [0.77, 0.94]), previous radiation (OR: 1.95 [1.34, 2.83]), and race—both "other" and White (ORs: 0.21 [0.07, 0.64], 0.33 [0.14, 0.74]).

For hepatitis, TAIL and FH initially find no risks, but a two-step model identifies age (OR: 0.980 [0.967, 0.994]) and liver metastasis (OR: 1.673 [1.075, 2.604]) as factors. Asian ethnicity also emerges as a significant risk in ARISg (OR: 2.841 [1.533, 5.267]) and GLMM (OR: 2.028 [1.292, 3.181]).

Conclusion: This study demonstrates how factors like demographics and medical history influence anemia and hepatitis risk, exposing the shortcomings of standard risk identification and the need for diverse data, like ARISg's findings, for full risk assessment. Using advanced methods like GLMM has honed risk precision. It emphasizes diverse ancestries' distinct risk profiles, advocating for varied data and analysis to enhance drug safety management.

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Enhancing Pharmacovigilance Through Methods-Driven Comparability of Cross-Data Source Analyses of Anemia and Immune-Mediated Hepatitis in NSCLC Patients Treated with PD-1/PD-L1 Therapies

Chu-Fang Lin[1], Svetlana Lyalina[1], Monika Kaul[1], Seid Hamzic[2], Martin Schaerer[2], Robert Walls[2], Yingjia Chen[1]

[1]*Genentech, South San Francisco, USA.* [2]*Roche, Basel, Switzerland*

Introduction: Pharmacovigilance involves continuous monitoring and assessment of drug safetysignals to ensure patient safety. The proposed comparative analysis aims to enhance pharmacovigilance practices by generating insights from an integrated database comprisingvarious sources, including clinical trials, real-world data, and spontaneous adverse event reporting systems. This approach addresses the significant challenge of comparability across different data sources due to variations in study design, patient populations, exposures, and database characteristics. By employing advanced methodologies such as propensity score weighting with SuperLearner and machine learning techniques, this analysis seeks to provide a more comprehensive and accurate assessment of drug safety. This improved comparability can lead to better safety signal management, more timely regulatory and clinical actions, and ultimately, improved patient outcomes.

Aim/Objective: This study adopts a G-computation framework with advanced statistical methods and machine learning techniques to demonstrate the feasibility of comparative analyses across diverse data types.

Methods: To assess the feasibility of our proposed method, we conducted a retrospective,secondary data use observational study assessing and comparing the risk of anemia and immune-mediated hepatitis in Stage IIIb/IV NSCLC patients treated with PD-1/PD-L1 drugs.

Results: Our study demonstrates that the proposed method significantly improves the balance of different cohorts, although the effectiveness in balancing cohorts fluctuated based on theweighting methods used, model specifics, and the patterns of missing data. Weighting was advantageous for its potential to yield a higher effective sample size than matching. For anemia, the estimated crude risks varied significantly across the data sources, with the TAIL study showing the highest risk, followed by Adverse Reaction Information System Global (ARISg), and Flatiron (FH) showing the lowest risk. After adjusting for cohort imbalances using propensity score weighting, the risks in ARISg increased slightly while the risk in FH remained relatively stable. Regarding hepatitis, the estimated crude risks were highest in ARISg, lower in TAIL, and lowest in FH. The adjusted risks post-weighting showed a similar trend, with ARISg maintaining the highest adjusted risk, while FH's risk remained stable.

	Source	Total patient	Crude Risk with 95% CIs	Adjusted Risk with 95% quantile Bootstrapping CIs
Anaemia	ARISg	2027	0.036 (0.033, 0.038)	0.055 (0.045, 0.067)
	Flatiron Health*	7288	0.0032 (0.0028, 0.0036)	0.0028 (0.0024, 0.0033)
	TAIL	619	0.126 (0.118, 0.134)	0.126 (0.118, 0.134)
Immune-mediated hepatitis	ARISg	2027	0.085 (0.074, 0.098)	0.068 (0.048, 0.097)
	Flatiron Health*	7288	0.006 (0.004, 0.008)	0.006 (0.004, 0.010)
	TAIL	619	0.016 (0.009, 0.030)	0.016 (0.009, 0.030)

Conclusion: The proposed methodology significantly enhances pharmacovigilance and safetyactivities by providing a comprehensive view of safety data across diverse sources. By improving the comparability of data from various sources, this approach can streamline current pharmacovigilance practices, making signal detection and evaluation in safety more reliable.

Additionally, this can lead to proactive risk management and more robust regulatorysubmissions and reviews. For patients and healthcare providers, the approach ensures earlier detection and management of adverse effects, improving patient outcomes and providingbetter treatment information. However, challenges such as data integration, harmonization of outcome definitions, and regulatory acceptance need to be addressed to fully realize these benefits. Detailed analytical methodologies and additional results will be presented at ICPE2024, "Methods in Pharmacoepidemiology/Analytical Methods" section, demonstrating the feasibility and effectiveness of this approach.

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Comprehensive Analysis of Heart Failure Management: Insights from Vision C+ registry

Shweta Todkar[1,2], Sonia Corbin[1,2], Floraise Lynda Tanguena[1,2], Hugo Lortie[3], Emmanuel Marier-Tétrault[4,5], Pierre Yves Turgeon[6], Lauren Basmadjian[7], Charaf Eddine Ahnadi[8], Serge Lepage[9], François Tournoux[4,5], Paul Poirier[1,6], Jacinthe Leclerc[1,2]

[1]Faculté de pharmacie, Université Laval, Québec, Canada. [2]Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval, Québec, Canada. [3]Université de Sherbrooke - Centre Hospitalier Universitaire de Sherbrooke, Québec, Canada. [4]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Québec, Canada. [5]Division de cardiologie, Département de médecine du Centre Hospitalier de l'Université de Montréal (CHUM), Québec, Canada. [6]Département de cardiologie, Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval, Québec, Canada. [7]Centre de recherche, Institut de Cardiologie de Montréal, Université de Montréal, Québec, Canada. [8]Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CHUS), Québec, Canada. [9]Département de médecine, Université de Sherbrooke, Québec, Canada

Introduction: Heart failure (HF), has impacted over 750,000 Canadians ≥40 years old, with new cases rising annually (1, 2). To enhance HF care, monitoring the effectiveness of management is crucial (3). While electronic medical records (EMR) provide valuable data, challenges such as non-interoperability and noncompliance with FAIR principles (findable, accessible, interoperable and reusable) persist (4, 5). In 1998, the Quebec Heart Failure Society created the Vision C+ platform, a web-based EMR designed to follow-up HF patients in clinics with the aim of enhancing quality of medical interventions and advancing our knowledge of HF while adhering to the FAIR principles (6, 7).
Aim/Objective: To provide a comprehensive analysis of HF management using data from the Vison C+ registry.
Methods: The Vision C+ Registry contains structured clinical data of patients treated for HF in 41 specialized clinics across the province of Quebec since 1998 (7). Data were generated during patient consultations with multidisciplinary team members. The registry is built with 34 other categories of variables such as demographics, cardiac and medical history, natural health products (NHP), medications etc. Patients are linked with a unique crypted identification number. Descriptive analysis was performed on data from 1998 to 2021.
Results: As of December 2021, the Vision C+ Registry included data from 64,131 patients (24% alive, 29% dead, 47% inactive). Mean age was 74 ± 16 years, 35% were female, 1% were followed for ventricular assist device, 2% for heart transplantation and 97% for various types of HF. Mean left ventricular ejection fraction (LVEF) was 37% with NYHA class II comprising the highest proportion at 49%. Prevalent comorbidities included diabetes (76%), hypertension (65%) and dyslipidemia (55%). Mean follow-up time was 1.5 years. The overall readmission rate was 6%, increasing in the recent years to 12% in 2019, 15% in 2020 and 13% in 2021. Additionally, 495 patients were using NHP and over the counter medicines. The most commonly used NHP categories were vitamins and minerals (30%), followed by amino acids and essential fatty acids (23%), and herbal remedies (8%). Notably, omega-3, glucosamine and vitamin D were the most commonly consumed supplements.
Conclusion: The Vision C+ registry is a valuable asset for advancing HF research. The comprehensive data provides valuable insights into HF management practices which are crucial for optimizing care and enhancing outcomes for HF patients.
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Virtual Interconsultations to a Clinical Pharmacy Service to Reduce Underreporting of Adverse Drug Reactions

Gladys Martha Delgado-Pérez, Nelly Delfina Mejía-Acosta, Rosalba Maekawa Ikehara, Cristopher Emanuel Dávila-Espinoza

Universidad Nacional Mayor de San Marcos, Lima, Peru

Introduction: National spontaneous reporting systems do not reflect the true rate of adverse drug reactions (ADRs).[1] Underreporting reaches 94%,[2] mainly due to lack of time and workload of healthcare professionals. [3, 4] Smartphone applications have facilitated the pharmacovigilance process in recent years.[4, 5]
Aim/Objective: To describe the virtual and paper-based three-period interconsultations, and to characterize the ADRs of virtual interconsultations.
Methods: Retrospective observational study. The number of SADRs sent by physicians from the Department of Medicine to the clinical pharmacy service of the Hospital Nacional de la Policía Nacional del Perú (HNPNP), between September 2019 and February 2020, was calculated. Which were compared with paper-based SADRs interconsultations in two previous periods. Traditional interconsultations were performed on paper by physicians during medical visits and were sent to the clinical pharmacy service while virtual interconsultations were via Google form (G-form®), which containing: I. Patient data; II. Principal diagnosis; III. SADRs; IV. Suspected drug; V. Notifier data (first and last name, specialty). Clinical pharmacists provided the access link via: QR code, MSM, email, WhatsApp®, Telegram®. The interconsultations via G-form performed were compiled in the Google Workspace "Spreadsheet". Both modalities, the ADRs were analyzed and reported to the Centro Nacional de Farmacovigilancia y Tecnovigilancia (CENAFyT). For causality and severity, the modified Karch and Lasagna algorithm was used; terminology for ADRs followed the MedDRA criteria and the Systems, Organs and Classes (SOC) classification. The study was approved by the HNPNP Ethics Committee.
Results: Fourteen physicians participated and reported a total of 39 SADRs through G-form, while paper SADRs interconsultations were 17 and 15 in two similar periods from September 2017 to February 2018 and September 2018 to February 2019, respectively. A total of 39 SADRs from the virtual interconsultations were reported to CENAFyT by clinical pharmacists, obtaining 77 ADRs; 54 (70.1%) were definite and likely, 11 (14.3%) serious events and 40 (51.9%)

type B. The most frequent clinical manifestation associated with ADR was: skin and subcutaneous tissue disorders (n = 22; 28.6%). The drugs causing the most ADRs were anti-infectives for systemic use (n = 40; 52%).

Conclusion: G-form is an alternative of virtual interconsultation for reporting SADRs. It doubled the number of interconsultations for ADRs compared to the traditional method. Relevant clinical manifestations were obtained from the reports submitted to CENAFyT.

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Concomitant Use of Antipsychotics and Progestogens: An Increased Risk of Reporting Galactorrhea?

Romain Barus[1], Claire De canecaude[1], Pauline Schiro[1], Christinea Damase-Michel[1], Louise Gaboriau[2], Benedicte Nobile[3], François Montastruc[1]

[1]Toulouse University Hospital, toulouse, France. [2]Lille University Hospital, Lille, France. [3]Montpellier University Hospital, Montpellier, France

Introduction: Galactorrhea induced by antipsychotics is a well-known adverse drug reaction that can impact the quality of life of patients. Cases of galactorrhea are also described with hormonal contraceptives containing only progestogen. We hypothesized that antipsychotics and progestogens might present a pharmacodynamic interaction, enhancing the risk of galactorrhea.

Aim/Objective: By using the French pharmacovigilance database, we described galactorrhea cases in women using both antipsychotics and progestogens and studied the potential drug-drug interaction (DDI) between those medications.

Methods: In the French pharmacovigilance database, we included reports of galactorrhea in women taking both antipsychotics and progestogens contraceptives. Drugs might be registered as suspected or concomitant. To detect DDI, we performed 1) an additive model based on the calculation of three reporting odds ratio and 2) the omega (Ω) shrinkage which is the observed-to-expected ratio measure. In the additive model, the sum of the ROR associated with antipsychotics and progestogens had to be lower that the ROR of the combination to generate a signal. In the Ω model, the detection criterion is $\Omega025 > 0$.

Results: Seven cases of galactorrhea were included. Mean age was 17 years old (IQR = 16.5-26.5). Progestogens implicated were: desogestrel (n = 1), etonogestrel extended-release (n = 3), and levonorgestrel (n = 3). Antipsychotics implicated were: risperidone (n = 2); olanzapine alone (n = 1) or with cyamemazine (n = 2), loxapine (n = 1), and zuclopenthixol (n = 1). In 3 cases, the adjunction of progestogens induced galactorrhea. Among those 3 cases, prolactinemia was increased in 2 of them (for the third, prolactinemia was unavailable). Concomitant use of antipsychotics and progestogens was associated with an increased risk of reporting galactorrhea (ROR = 86.3; CI95%[40.1-185.6]). Both additive model and Ω model ($\Omega = 1.6$; $\Omega025 = 0.5$) suggested a DDI regarding the risk of galactorrhea between antipsychotics and progestogens.

Conclusion: In women, concomitant use of antipsychotics and contraceptives progestogens increased the risk of reporting galactorrhea. Clinicians should be aware of this potential DDI.

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Knowing Me, Knowing You—Lessons Learned from Three European Studies on European Medicines Agency's Risk Communication

Ella van Vliet[1], Anna Birna Almasdóttir[2], Shahab Abtahi[3], Christos Kontogiorgis[4], Elita Poplavska[5], Mitja Kos[6], Inês Ribeiro-Vaz[7], Juan Erviti[8], Lies Lahousse[9], Teresa Leonardo Alves[1]

[1]National Institute for Public Health and the Environment, Bilthoven, Netherlands. [2]University of Copenhagen, Copenhagen, Denmark. [3]Utrecht University, Utrecht, Netherlands. [4]Democritus University of Thrace, Alexandroupolis, Greece. [5]Riga Stradins University, Riga, Latvia. [6]University of Ljubljana, Ljubljana, Slovenia. [7]University of Porto, Porto, Portugal. [8]Servicio Navarro de Salud, Pamplona, Spain. [9]Ghent University, Ghent, Belgium

Introduction: To minimise the potential negative effects of using medicinal products, the European Medicines Agency (EMA) issues regulatory risk communication. These consist of routine risk minimisation measures (rRMM), such as specific product information, and when necessary additional RMMs (aRMM) such as pregnancy prevention programmes (PPPs), or Direct Healthcare Professional Communications (DHPC) (1). EMA's Pharmacovigilance Risk Assessment Committee oversees the safety of medicines and recommends the implementation of RMMs. The implementation of such risk communication takes place nationally and can show differences across countries.

Aim/Objective: The studies aimed to assess the impact of RMMs and other risk communication put forward by the EMA on patients and healthcare professionals (HCPs), across selected EU countries.

Methods: In total, three European studies were performed, funded by EMA. All studies adopted a mixed methods approach using cross-sectional surveys among patients and HCPs to investigate awareness, knowledge and adherence to the measures combined with interviews to gain context. Studies were performed in 6-8 countries, with a varied geographical distribution. Cases studied were: 1) PPP for teratogenic effects of oral retinoids (2), 2) PPP for teratogenic effects of valproate related products (3), and 3) risk communication on thrombosis with thrombocytopenia syndrome (TTS) for COVID-19 adenoviral vaccines (4).

Results: A total of 1277 HCPs responded to the oral retinoids survey, 1202 to the valproate survey and 915 to the COVID-19 vaccine questionnaire. As to public surveys, 298, 323 and 3794 responses were collected in the three studies, respectively. Risk awareness for these products was high among patients and HCPs in all three cases, both for well-known and for recently identified risks. However, use of educational materials and adherence by patients and HCPs to PPPs for valproate and oral retinoids were moderate to low and varied across countries. While attitudes towards the general use of vaccines remained positive, reports about TTS did affect negatively the willingness of public respondents to be vaccinated with adenoviral

vaccines. There was moderate to high awareness of aRMMs for TTS among HCPs. Facilitators and barriers for implementation of (a)RMMs were also identified.

Conclusion: The awareness about and dissemination of the risks (both new, e.g., TTS, or well established, e.g., teratogenic effects) associated with oral retinoids, valproates and COVID-19 adenoviral vaccines seem to have been effective for patients and HCPs. Yet, the application and adherence to PPPs proved to be intricate. Easily accessible, applicable and understandable materials are preferred by HCPs and patients.

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Follow-Up of Pure Red Cell Aplasia Associated to Hemax®, a Biosimilar Epoetin Alfa

Maria Florencia Amato, Lucia Tovar, Maria Clara Peralta, Roberto Alejandro Diez

Biosidus SAU, Buenos Aires, Argentina

Introduction: Pure Red Cell Aplasia (PRCA) is a serious adverse effect, believed to arise from the induction of neutralizing antibodies against erythropoietin in the course of therapy with epoetin or other erythropoiesis stimulating agents. Epoetin alfa (Hemax®) is a similar biological product (SBP) containing epoetin alfa, marketed in Argentina in 1990 and subsequently, in other 37 developing countries. Information about safety of SBP outside developed countries is very limited and the focus on specific drug products is frequently difficult due to limitations in the follow up or access to patient´s data.

Aim/Objective: In 2008 we presented the first evaluation of PRCA among patients treated with Hemax®; the aim of this research is to update the PRCA cases during 16 additional years of surveillance.

Methods: Retrospective search in the Biosidus' database for cases reported as PRCA, diagnosed according to clinical data, hematologic evaluation, and detection of anti- erythropoietin antibodies by a validated radio-immunoprecipitation method.

Results: Until 2022, 17 cases of PRCA have been reported to ANMAT as a defined adverse effect of Hemax®. Ten patients were female. The age range was from 31 to 83 years old, mean ± SD 67.7 ± 17.7 years, median 56 years. All cases presented anemia detected as loss of efficacy after several months of successful treatment, with bone marrow findings consistent with erythroid progenitors decrease. All presented antibodies against erythropoietin, with titers between 1/100 and 1/10,000; no neutralizing test was available to assess biological activity of the antibodies. All cases corresponded to patients administered SC epoetin and showed very low values of blood erythropoietin (8.8 ± 12.5 mIU/ml, median 6 mIU/ml). According to Hemax® sales, transformed in DDD, the cumulative rate of PRCA associated to Hemax® is 0.011 cases per 100,000 patient-years. The rate for Thai patients is higher than the worldwide value, reaching 3.431 cases per 100,000 patients-year since 1998, time of its launching in Thailand. Though some risk factors have been described, including genetic factors such as specific MHC haplotypes (specifically HLA-B*46:01:01:01 and DRB1*09:01:02:01, Suttichet *et al*, 2023) or STAT-3 mutations, no data of that factors are available for our patients. Until 2023, Biosidus´ Drug Safety Unit received 20 presumptive PRCA cases from Thailand, without gender prevalence. Likewise, age factors are not observed. During this year, a protocol is being designed in conjunction with the local partner to determine the causes of this event.

Conclusion: Evaluation of PRCA risk associated to Hemax® yielded results consistently in the same order of magnitude than innovator ESA products and below the peak induced by changes in the innovator epoetin alfa. A deeper analysis is required to assess risk factors, such as genetic determinants, and improve risk minimization.

Of the total cases received by December 2023 (27), half were from Thailand.

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Vitreous Detachment and Teriparatide (Osteofortil): Case Report and Literature Review

Maria Florencia Amato[1], Lucia Tovar[1], Maria Clara Peralta[1], Roberto Alejandro Diez[1], Denise Medrano[2]

[1]Biosidus SAU, Buenos Aires, Argentina. [2]Universidad de Buenos Aires, Buenos Aires, Argentina

Introduction: Teriparatide has been approved for almost 20 years with a favorable benefit-risk balance for it. We present, to our knowledge, the first reported case of bilateral vitreous detachment associated with Teriparatide.

Aim/Objective: To identify the association between the use of Teriparatide and the adverse event, we performed a pharmacovigilance analysis by literature review and by consulting physicians specialist in the subject. A search of PubMed and International Pharmaceutical Abstracts was conducted using the Medical Subject Headings terms teriparatide, vitreous detachment, and no results were found.

Methods: The possible side effects of this drug have been extensively studied over the years, still the association of vitreous detachment with Teriparatide has not been established in current literature.

Results: A 57-year-old woman, with severe osteoporosis under calcium, vitamin d and teriparatide (20 mcg daily by SC injection) developed bilateral vitreous detachment after six months of treatment. The symptoms started suddenly with photopsias only in the left eye. After an early consultation, she continued under treatment but 2 days later, after increase of symptoms, which became bilateral, the treating physician decided to discontinue teripatide with only ophthalmological control. Upon cessation of the drug, and a week control the patient's symptoms remitted, and after 24 days without medication she received the oftalmological discharge, with her visual perimetry restored ad integrum. Intraocular pressure was 16 mm Hg in both eyes and visual acuity was 10/10. However, and due to the clinical history

of the patient, and the need of treatment, the treating professionals decide to re-expose her to the drug.
To obtain further information in this regard, we consulted specialist ophthalmologists. They suggest the event may be associated the event with mannitol, an excipient in the formulation of the drug. With this found, we proceeded to confirm this information about mannitol in bibliographic sources (PubChem, 2022; Wishart et al, 2017; Rowe et al, 2009)
Conclusion: The possibility of a causal relationship between teriparatide and the adverse event cannot be ruled out, even though our hypotheses suggest that the cause of the event would be one of the formulation excipients, the mannitol, and not the teriparatide itself. Another hypothesis we shuffled, also related with the mannitol, is that an error could have been made in the method of administration, a blood vessel may have been injured, generating the entry of mannitol into the bloodstream, and thus exacerbating its effect on the intraocular pressure.
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Adverse Events Reported with Medical Cannabis During the French Experimentation

Cécile Chevallier[1], Basile Chrétien[2], Anne Batisse[3], Louise Gaboriau[4], Choucki Chenaf[5], Emilie Monzon[6], Nathalie Richard[7], Marine Auffret[1]

[1]Hospices Civils de Lyon, Lyon, France. [2]CHU de Caen, Caen, France. [3]AP-HP, Paris, France. [4]CHU de Lille, Lille, France. [5]CHU de Clermont-Ferrand, Clermont-Ferrand, France. [6]ANSM, Saint-Denis, France. [7]ANSM, Saint Denis, France

Introduction: Since 2021, the French drug agency (Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM)) has implemented an experimentation concerning medical cannabis for five indications (neuropathic pain refractory to available therapies; certain forms of severe, drug-resistant epilepsy; certain intractable symptoms related to cancer or its treatment; palliative situations; painful spasticity due to multiple sclerosis or other central nervous system pathologies). Medicines contained cannabidiol (CBD) or delta-9-tetrahydrocannabinol (THC), or both. A registry was implemented to increase the number of notifications of adverse events (AEs) related to medical cannabis.
Aim/Objective: The objective of this study is to describe safety data collected during the first two years of this experimentation.
Methods: Data were extracted from the registry and the French pharmacovigilance database between March 26, 2021 and March 31, 2023. Both pharmacovigilance and addictovigilance records were analyzed.
Results: Out of 2,512 patients treated with medical cannabis, 1,013 patients (40.3%) presented at least one AE. Nearly 60% of AEs occurred during the titration phase. Across all indications, the main AEs were neurological (37.2%), digestive (16.9%) and psychiatric (15.2%). Seventy-five patients (3.0%) presented a serious AE. Concerning serious AEs, the median dose of CBD reported was 40 mg/d (IQR 20-80) and the median dose of THC reported was 15 mg/d (IQR [0.75–20]).. Among the serious cardiovascular AEs, 6 cases of acute coronary syndromes were reported and concerned patients aged over 69 with underlying cardiovascular disease for 5 of them. Among psychiatric disorders, 8 cases of suicidal thoughts with one suicidal attempt were reported, half of which occurred in patients with no known psychiatric history. Were also reported 3 cases of aggravation of epilepsy or tonic-clonic seizures, including one sudden unexpected death in epilepsy, one case of cannabis-induced hyperemesis syndrome resulting in hospitalization and one case of acute pancreatitis. Five patients presented a withdrawal syndrome and three cases of tolerance were described in CBD only and THC-treated patients. A case of misuse of THC inflorescences was reported in a pain patient with a history of recreational cannabis use and misuse of opioid analgesics.
Conclusion: Few serious AEs have been reported despite a very close monitoring of the safety of medical cannabis. The safety profile consisted mainly in neurological, digestive and psychiatric AEs, with most AEs occurring during the titration phase. These are expected AEs, given the pharmacological mechanism of action of cannabis. Only one case of misuse of medical cannabis have been reported.
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Cutaneous Adverse Events Associated with Enfortumab Vedotin: A Critical Analysis of French Pharmacovigilance Data

Julien Mahé[1], Bénédicte Lebrun-Vignes[2], Christine Le Beller[3], Paola Sanchez-Pena[4], Nassir Mirfendereski[1], Marion Allouchery[5], Marie-Christine Perault-Pochat[6]

[1]Pharmacologie Clinique et Vigilances, CHU de Poitiers, Poitiers, France. [2]Centre Régional de Pharmacovigilance, Service de Pharmacologie Médicale, Hôpital Pitié-Salpêtrière, GH APHP. Sorbonne Université, Paris, France. [3]Department of Pharmacovigilance, Hôpital Européen Georges Pompidou, AP-HP. Centre–Université Paris Cité, Innovative Therapies in Haemostasis, INSERM, Paris, France. [4]Service de pharmacologie médicale, centre régional de pharmacovigilance de Bordeaux, CHU de Bordeaux, Bordeaux, France. [5]Pharmacologie Clinique et Vigilances, CHU de Poitiers, Université de Poitiers, Poitiers, France. [6]Pharmacologie Clinique et Vigilances, CHU de Poitiers, Laboratoire de Neurosciences Expérimentales et Cliniques, Inserm U1084, Université de Poitiers, Poitiers, France

Introduction: Enfortumab vedotin (EV), a Nectin-4 directed antibody drug conjugate with the cytotoxic agent Monomethyl auristatin E (MMAE), is approved as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma. Cutaneous adverse reactions (CARs) are commonly associated with EV but sometimes confused with drug allergic hypersensitivity. As Nectin-4 is expressed in the skin, CARs may be related to Nectin-4-targeted MMAE binding, rather to an immune-related mechanism.
Aim/Objective: To analyze CARs diagnosis recorded in the French pharmacovigilance database (FPVD).
Methods: We performed a retrospective analysis of CARs registered in FPVD with EV from 1st July 2021 to 30 December 2023. Data collection included demographic characteristics (age, gender) and skin disorders characteristics (time to onset, clinical features, severity, biopsy results, associated systemic signs, outcome, management, terms used for coding).
Results: Our study included 83 patients with an average age of 70 years (standard deviation 8.5), and a sex-ratio M/F of 2.8. Half of the cases were serious including 8 deaths. Despite various clinical features (46 different terms used), most included erythema (24 cases) and blistering (10 cases). The mean time to onset was 12 days. Systemic involvement was associated in 36% of CARs, such as blood disorders (11%) or acute renal failure (8%). Nearly half of cases (53%), displayed signs of direct cutaneous toxicity from EV. Misdiagnoses were found in 6 cases: 3 cases considered as symmetrical drug-related

intertriginous and flexural exanthema and 3 cases considered as toxic epidermal necrolysis. Most cases (68%) resolved, often with dermocorticoids. Whereas EV dosage was often reduced in non-serious cases, EV treatment was stopped in serious cases.

Conclusion: Misdiagnosis of EV-induced toxic CARs was frequent. Most of CARs shared stereotyped features and similar time to onset. Skin detachment associated with keratinocyte necrosis, and dysmaturation on histology argue for direct cutaneous toxicity of EV. This is a form of chemotherapy skin toxicity observed with other cytotoxic anticancer drugs defined as "toxic erythema of chemotherapy". [1] However, CARs appear to be more severe with EV and potentially life-threatening. [2] Our study highlights the importance of a multidisciplinary decision when facing these complexes CAR. Indeed, a recent clinical trial demonstrated the benefits of combining EV with pembrolizumab, but with increased rates of CARs. [3]

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Venlafaxine and Reversible Cerebral Vasoconstriction Syndrome: Data from VigiBase® and Literature.

Brahim AZZOUZ, Maxime MOINY, Jed HADJOUDJ, Emmanuelle HERLEM

Regional Pharmacovigilance Centre, Reims University Hospital, Reims, France

Introduction: Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) approved to manage symptoms of depression, social phobia, and panic disorder. A case of reversible cerebral vasoconstriction syndrome (RCVS) after venlafaxine exposure was notified to our Regional Pharmacovigilance Centre. Only 2 similar cases were registered in the French pharmacovigilance database. Among all antidepressant, RCVS is only listed in the Product Infomations of sertraline, a selective serotonin reuptake inhibitor (SSRI). In this context, we investigated the WHO pharmacovigilance database and published case reports.

Aim/Objective: To describe the risk of RCVS with venlafaxine.

Methods: We described all Individual Case Safety Reports (ICSRs) with venlafaxine registered in VigiBase® of the RCVS from the inception of the database to March 28, 2024. A disproportionality analysis was performed. Cases were identified using the MedDRA® preferred term "reversible cerebral vasoconstriction syndrome", non-cases were all other adverse drug reactions (except RCVS). Sertraline was used as a positive control. Reporting Odds Ratios (RORs) and their 95% Confidence Intervals were calculated. Published cases of RCVS associated to venlafaxine intake were also reviewed.

Results: In VigiBase®, 35 ICSRs met our research criteria. The average age of patients was 43 years (range 20 - 55 years), and 83% of patients were women. All cases were severe, as expected. Venlafaxine was discontinued in 30 patients and the outcome was favorable in 27/30 ICSRs. The ROR of the RCVS was 18.7 (13.6 - 25.6) with sertraline and 19.5 (13.9 - 27.3) with venlafaxine. We also found 3 published case reports [1–3]. The age of the patients ranged from 45 to 55 years, 2/3 were women. The outcome was favorable after drug withdrawal and symptomatic treatment (nimodipine or verapamil).

Conclusion: Venlafaxine may cause RCVS. The disproportionality analysis highlights a safety signal. Prescribers should be Prescribers should be sensitized to this risk. According to reviews dealing with RCVS [4], sympathomimetic and serotonergic vasoactive agents are risk factors. SSRIs and SNRIs are serotonergic vasoactive agents. All Summary Product Characteristics of SSRIs and SNRIs should list this risk.

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Skin Ulcers at Injection Sites Under Interferon-Beta 1a in a Multiple Sclerosis Patient: Case Report

Maria Florencia Amato[1], Roberto Alejandro Diez[1], Maria Clara Peralta[1], Lucia Tovar[1], Denise Medrano[2]

[1]Biosidus SAU, Buenos Aires, Argentina. [2]Universidad de Buenos Aires, Buenos Aires, Argentina

Introduction: Interferon β-1a (IFN-β 1a) represent first-line therapy for multiple sclerosis (MS) with immunomodulatory effects. It´s been in the market for 25 years and has proven to be an efficacious drug capable of reducing rate and severity of relapses, besides improving disease parameters, measured by MR imaging techniques.

Aim/Objective: To determine the causal relationship between interferon beta 1a and skin lesions at injection sites, including necrosis and ulcers, in a patient treated with Blastoferon for multiple sclerosis 7 months after initiation of treatment.

Methods: We performed a pharmacovigilance analysis by literature review and by consulting a group of specialists. A search of PubMed and International Pharmaceutical Abstracts was conducted using the MeSH terms Interferon β-1a with skin ulcers, skin lesions, hypersensitivity reaction. We found several case reports, one systematic review which indicate that skin lesions at injection sites under IFN-β 1a rarely occur, but they must be considered (Faghihi et al, 2015; Casoni et al, 2003)

Results: We present the case of a 69-year-old male patient, with a late diagnosis of MS, who developed skin ulcers at injection sites after 7 months of treatment with this agent (44 μg, thrice weekly, subcutaneous injection). The cutaneous lesions started as bruises at application sites on the legs that 20 days later evolved into ulcers. He continued under treatment rotating application sites into arms but after visualizing the same reaction the treating physician decided to discontinue IFN-β 1a. Meanwhile a biopsy of the lesions was performed and evidenced in deep skin tissue a dense inflammatory infiltrate (predominantly polymorphous nuclear) and necrosis affecting medium caliber blood vessel. Despite the fact that it was not possible to test neutralizing antibodies against IFN-β 1a (NABs) a possible Arthus reaction or a type III hypersensitivity reaction may have occurred, in which the role of NABs in the development of the skin lesions has to be consider.

Conclusion: Even though it was not possible to test neutralizing antibodies against IFN-β 1a (NABs) a possible Arthus reaction or a

type III hypersensitivity reaction may have occurred, in which the role of NABs in the development of the skin lesions has to be consider.

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Skin Papilloma after Upadacitinib Exposure: Data from VigiBase®

Brahim AZZOUZ[1], Clélia VANHAECKE[2], Imman ABDELOUAHAB[1], Aurore MOREL[1]

[1]Regional Pharmacovigilance Centre, Reims University Hospital, Reims, France. [2]Department of Dermatology, Reims University Hospital, Reims, France

Introduction: Upadacitinib is a selective Janus kinase 1 inhibitor approved for use in a variety of dysimmune diseases: rheumatoid arthritis (RA), ankylosing spondylitis, atopic dermatitis (AD), hemorrhagic rectocolitis, and Crohn's disease. One case of cutaneous papilloma secondary to upadacitinib (in the setting of AD) was reported to our regional pharmacovigilance center. No similar case was found in the French pharmacovigilance database. In this context, we investigated the WHO pharmacovigilance database.
Aim/Objective: To describe the risk of skin papilloma with upadacitinib using VigiBase®.
Methods: We analyzed all Individual Case Safety Reports (ICSRs) registered in VigiBase® of skin papilloma with upadacitinib from the inception of the database to March 28, 2024. A disproportionnality analysis was performed. Cases were identified using the MedDRA® Preferred Term « skin papilloma », non-cases were all other dermatologic diagnoses (except skin papilloma). Reporting Odds Ratio (ROR) and its 95% Confidence Intervall were calculated.
Results: On March 28, 2024, we identified 45,520 ICSRs implicating upadacitinib in VigiBase®, of which 5,900 were cutaneous adverse effects. Twenty-seven ICSRs involved cutaneous papilloma after upadacitinib exposure. The average age of patients was 47 years (rage 17–85 years), 67% were women. Therapeutic indications (available for 24 ICSRs) were RA (n = 14), AD (n = 6), Psoriatic Arthitis (n = 1), Crohn's Disease (n = 1), Ankylosing Spondylitis (n = 1) and Haemorrhagic Retrocolitis (n = 1). Thirteen cases were considered serious. Time to onset (when mentionned) ranged from 4 days to 5 months. The overall ROR for upadacitinib was 5.2 (3.5–7.5). The ROR for upadacitinib used in RA was 10.82 (6.39–18.32), the ROR for upadacitinib used in AD was 19.79 (8.84–44.32).
Conclusion: Upadacitib may induce skin papilloma. The female predominance observed here is consistent with epidemiologic data in dysimmune diseases. The disproportionality analysis highlights a safety signal, with the highest signal observed for upadacitinib in AD. Prescribers should be sensitized to this risk. Although the risk is rare, we recommend regular skin examinations during the first year of treatment. To our knowledge, only one case report has been published (20-year-old male). Upadacitinib was used for AD and the time to onset was 2 months [1].

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Are Serious Adverse Events Reported in the Quebec Population Treated for Heart Failure?

Floraise Lynda Tanguenan[1,2], Shweta Todkar[1,2], Maude Lavallée[1,2], Sonia Corbin[1,2], Julie Méthot[1,2], Marie-Ève Piché[2,3], Anick Bérard[4], Serge Lepage[5], Charaf Eddine Anhadi[5], François Tournoux[6], Anique Ducharme[7], Jacinthe Leclerc[1,2]

[1]Faculty of Pharmacy, Université Laval., Québec, Canada. [2]Research Centre of the Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval., Québec, Canada. [3]Faculty of Medicine, Université Laval., Québec, Canada. [4]Centre de recherche du Centre hospitalier universitaire Sainte-Justine (CHU Ste-Justine), Faculté de pharmacie, Université de Montréal, Montréal, Canada. [5]Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CRCHUS), Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Centre de recherche du CHUS (Sherbrooke) Collaboration pour l'efficacité en diagnostic., Sherbrooke, Canada. [6]Faculty of Medicine, Université de Montréal., Montréal, Canada. [7]Montreal Heart Institute, Faculty of Medicine, Université de Montréal., Montréal, Canada

Introduction: More than 750,000 Canadians live with HF. Between 2015-2016, more than 22,000 quebecers were diagnosed with HF and among them more than 18,000 people died, representing a mortality rate of 11.5%. The elderly is the most affected, in addition to being at risk of adverse events (AEs) given their comorbidities and the multitude of medications they receive during treatment. Since the implementation of Vanessa's Law by Health Canada, reporting of serious AEs is mandatory for hospitals. However, most AEs, whether serious or not, are not reported to health authorities, thus hindering knowledge of the risk-benefit ratio of drugs. [1–6]
Aim/Objective: 1) To measure the difference between serious AEs that occurred vs. those reported to the health authorities. 2) To determine the factors associated with the reporting of serious AEs, and specifically fatal AEs, to health authorities.
Methods: This is a quantitative retrospective cohort study with data from 1998 to 2021. Data will be extracted from the Vision C+ Registry, contains the electronic medical records of 64,129 patients who are or have been followed up in Quebec heart failure clinics. Descriptive analyses (mean, median, minimum-maximum, proportions) will be performed to characterize the study population. An average of the number of serious AEs reported and not reported to health authorities will be calculated annually. To meet our 2nd objective, Student's t-tests and chi-square tests will be performed.
Results: EXPECTED RESULTS. Preliminary data from our laboratory (including clinical data from Institut Universitaire de Cardiologie et Pneumologie de Quebec-Université Laval) suggest that less than 1% of AEs are reported to Health Canada. Moreover, the discrepancy between serious AEs that have occurred and those reported to Health Canada would be high.
Conclusion: Pharmacovigilance studies offer an opportunity to assess the safety profile of drugs in clinical practice. To date, there is still a huge need for knowledge in drug monitoring. Because Heart failure patients are vulnerable, it's vital to improve the risk-benefit ratio of post-marketing drugs.

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Evaluation of Oncology Medicinal Products Risk Minimisation Measures: a Review of Studies Registered in the European Medicines Agency (HMA-EMA) Catalogue

Jorge Monteiro[1], Diogo Almeida[1,2], João Paulo Fernandes[1,2,3], Bruno Sepodes[1,2], Carla Torre[1,2]

[1]Faculdade de Farmácia, Universidade de Lisboa, Lisbon, Portugal. [2]Laboratory of Systems Integration Pharmacology, Clinical and Regulatory Science, Research Institute for Medicines of the University of Lisbon (iMED.ULisboa), Lisbon, Portugal. [3]INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon, Portugal

Introduction: The Good Pharmacovigilance Practices (GVP) guideline are a set of measures drawn up to facilitate the performance of the safety monitoring of medicines in the European Union. Module XVI outlines that planning and implementing risk minimisation measures (RMM) and assessing their effectiveness are essential elements of risk management. Pharmacovigilance activities play a crucial role in oncology, given the potential for toxicity, narrow therapeutic windows and strict dosing schedules associated with many of the medicinal products used.
Aim/Objective: To analyze post-authorization studies aimed at evaluating the effectiveness of RMM (routine and additional) of oncology medicinal products, registered in the Heads of Medicines Agencies and the European Medicines Agency (HMA-EMA) Catalogue of real-world data studies (RWD Catalogues).
Methods: All RMM effectiveness evaluation studies registered in the HMA-EMA RWD Catalogues up to February 2024, in regard to medicines categorized under the Anatomical Therapeutic Chemical code "L (Antineoplastic and Immunomodulating Agents)" and "V10 (Therapeutic Radiopharmaceuticals)", with a therapeutic indication in oncological medical conditions, were reviewed. Data extracted from submitted protocols and study reports included medicine information, study design, timelines, target population and objectives, types of RMM evaluated, data collection methods, process and outcomes indicators and reported effectiveness.
Results: Of the 1280 studies registered in the HMA-EMA RWD Catalogues, 21 eligible studies evaluating the effectiveness of RMM of oncology medicinal products were reviewed. Seventeen studies (81%) were cross-sectional surveys, 57% (n = 12) were aimed at Healthcare Professionals as their target population and 86% (n = 18) used primary data sources. Regarding the type of RMM evaluated, 81% (n = 17) evaluated additional, 5% (n = 1) evaluated routine and 14% (n = 3) evaluated both. Ninety percent (n = 19) assessed process indicators, 5% (n = 1) assessed outcome indicators and 5% (n = 1) assessed both. Fifteen studies had a study report available. Of those, regarding the effectiveness of RMM, 53% (n = 8) were deemed effective, 33% (n = 5) were inconclusive and 13% (n = 2) were classified as ineffective.
Conclusion: Most analyzed studies were cross-sectional surveys, evaluated additional RMMs and assessed process indicators, with only one assessing both process and outcome indicators. Half of the studies with available results were reported as effective and a third of them were inconclusive. The GVP guideline (Module XVI) recommends outcome indicators (safety outcomes) as the ultimate measure of success of a risk minimisation programme, with process indicators complementing the assessment of outcome indicators. Continuing to develop future regulatory guidance regarding effectiveness evaluation of RMM could be beneficial in reaching better established measures of success.
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Opioid Analgesic-Associated Adrenal Insufficiency : A Dual-Approach Pharmacovigilance Study

Nassir Mirfendereski[1], Marion Allouchery[1], Julien Mahé[1], Aurore Morel[2], Marion Lepelley[3], Marie-Christine Perault-Pochat[4]

[1]Pharmacologie Clinique et Vigilances, CHU Poitiers, Poitiers, France. [2]Regional Centre of Pharmacovigilance and Pharmacoepidemiology, Reims University Hospital, Avenue du General Koenig, Reims, France. [3]Centre Régional de Pharmacovigilance - Addictovigilance CHU de Grenoble-Alpes, Grenoble, France. [4]Pharmacologie Clinique et Vigilances, CHU de Poitiers, Laboratoire de Neurosciences Expérimentales et Cliniques, Inserm U1084, Université de Poitiers, Poitiers, France

Introduction: Opioid-induced adrenal insufficiency (OIAI) is an unexpected adverse reaction but has been described in case series, with varying prevalence rates (6,2-66%) (1-2). Most data concern opiate substitution and little is known about opioid analgesic-induced adrenal insufficiencies.
Aim/Objective: We aimed to further describe OIAI patterns.
Methods: All cases of adrenal insufficiencies involving at least 1 opioid analgesic (OA) coded as suspected or interacting drug and reported up to 31 December 2023, were extracted from the French pharmacovigilance database (FPVD). After a description of the OIAI patterns, disproportionality analyses were performed in the WHO pharmacovigilance database (VigiBase®) according to OA type, with all analgesics as comparator group. Reporting odds ratios (ROR) and their 95% confidence intervals (95% CI) were estimated.
Results: A total of 15 OIAI cases were included in this study. Sixty percent were female, the median age was 49 years (interquartile range, 62-44). All cases were considered as serious. Morphine was the most frequently reported (37%), followed by fentanyl (16%) and oxycodone (16%). OA was the only suspect in 10 cases (66%). The mean morphine equivalent (MME) administered was 62.5mg (min-max., 10-320mg), with 86% of patients being treated for cancer-associated pain. The mean time to onset was 303 days (min-max., 1-1100). Hypocortisolemia was reported in 9 cases (60%), ACTH levels in 8 cases (53%), and cosyntropin test in 3 cases (20%). Normal pituitary MRI was found in 4 cases (27%). OA was withdrawn in 12 cases (80%), leading to full recovery of OIAI in 50% of cases. Twelve cases (80%) required hydrocortisone treatment. Significant disproportionality emerged for all OAs with all other analgesics as comparators (ROR 1.78; 95% CI [1.43-2.22]) and strong OAs, with all other analgesics excluding weak OAs (ROR 1.92; 95% CI [1.52-2.44]). Weak OA were not associated with higher reporting of adrenal insufficiency (ROR 1.1; 95% CI [0.79-1.51]).

Conclusion: Our data were consistent with previously published literature with varying onset times and OA doses with a lowest daily MME limit of 60mg (3). The higher reporting of adrenal insufficiencies in VigiBase® for strong OA only provides perspectives for underlying mechanisms. Indeed, this may be related to higher affinity of strong OA for opioid receptors in adrenal gland than weak opioids. Misdiagnosis of OIAI is also common and sometimes only symptoms can be reported in pharmacovigilance databases. Due to the rate of OA prescription, beyond their well-known risks, clinicians should be aware of OIAI, whatever strong OA dosage and treatment duration.

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Implementing an Active Surveillance Study of Patients Treated with a Tenofovir/Lamivudine/Dolutegravir (TLD) Regimen for HIV in Mozambique

Merana Mussa[1], Tania vuyeya Sitoie[1], Elizabeth Teketel[2], Eunice Dias Seni[3], Kisera Nereah[4], Kate Kikule[5], Irenio Gaspar[6], Jamal mario Paulino[6], Abramo Lemos[6], Stefia vilanculos[6], Andy Stergachis[7], N Damaraju[7]

[1]1. ANARME, IP, Maputo, Mozambique. [2]USAID MTaPS, Addis Ababa, Ethiopia. [3]USAID MTaPS, Maputo, Mozambique. [4]USAID MTaPS, Nairobi, Kenya. [5]USAID MTaPS, Arlington, USA. [6]National HIV/AIDS Program, Maputo, Mozambique. [7]4. School of Pharmacy and Public Health, University of Washington, seattle, USA

Introduction: More than 2 million people in Mozambique are living with HIV, about 60% of them women [1]. In 2018, Mozambique adopted the WHO recommended tenofovir/lamivudine/dolutegravir (TLD) regimen as first line HIV treatment. However, the country's national medicines regulatory authority, the Autoridade Nacional Reguladora de Medicamentos, Instituto Publico (ANARME, IP), did not have an active surveillance system to conduct WHO recommended active safety monitoring for adverse events (AEs).

Aim/Objective: Implementation of an active surveillance monitoring (ASM) study to monitor AEs in patients on a tenofovir/lamivudine/dolutegravir (TLD) regimen to support the effectiveness of Mozambique's public health programs in improving the process of care and outcomes for people living with HIV.

Methods: ANARME, IP and the HIV program in collaboration with the USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program designed and implemented the ASM of persons living with HIV patients who were being managed with TLD in nine sentinel sites from March 2020 to February 2022. This involved stakeholder coordination to develop the study protocol and standard operating procedures for data collection, training provincial focal persons, conducting causality assessments, and regular site visits to ensure protocol adherence and data quality [2]. MTaPS adapted and deployed the online Pharmacovigilance Monitoring System (PViMS) tool at study sites for efficient patient enrollment, data collection, and analysis, and conduct causality assessments [3].

Results: The study successfully achieved its objective of characterizing the AEs and adverse drug reactions (ADR) profiles among patients using TLD while also strengthening healthcare workers capacity to conduct ASM studies and ANARME, IP technical skills to conduct ASM, including causality assessments. Despite challenges such as limited personnel capacity to take on additional PV responsibilities and the COVID 19 pandemic, the targeted enrollment was met, and results showed good tolerability and safety of the TLD regimen [2]

Conclusion: Mozambique now has locally relevant data on the overall safety of the TLD regimen, and it has demonstrated its ability to implement ASM. Local ownership through the engagement of ANARME, IP and public health programs was vital to the success. Mozambique should consider digitizing its PV systems, training more healthcare personnel in PV, and using the study's experience to improve patient care outside of the HIV program.

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Ocrelizumab (Ocrevus(r)) Induced Neutropenia: Study in the French Pharmacovigilance Database

Sylvine PINEL[1], Roxane GOULAM[2], Sixtine GINISTY[1]

[1]Regional pharmacovigilance center Paris CHU Saint-Louis, Paris, France. [2]Regional pharmacovigilance center Paris CHU La pitié SalpétrièrePitié, Paris, France

Introduction: Ocrelizumab is a monoclonal antibody that targets the CD20 protein expressed on the surface of B lymphocytes involved in multiple sclerosis (relapsing-remitting and primary progressive), thereby reducing inflammation and myelin sheath degradation. The adverse effects expected with its use are infections, infusion-related reactions and neutropenia

Aim/Objective: Characterize neutropenia occurring during treatment with ocrelizumab.

Methods: Retrospective analysis of neutropenia cases [Hight Level Term neutropenia MedDRA classification] recorded in the French pharmacovigilance database, where ocrelizumab is the only suspected drug, from the date of marketing to March 01, 2024.

Results: 34 cases of neutropenia were recorded with ocrelizumab as the only suspect drug (agranulocytosis in 33 cases), in 24 cases neutropenia led to hospitalization. The median age of patients was 36 years (24-57) and the sex ratio was 0.26. The number of lines of previous ocrelizumab treatment was 4 (n = 1), 3 (n = 4), 2 (n = 2), 1 (n = 6), 0 (n = 7), unkown = 14. The median time (days) to onset of neutropenia after the last injection was 90, the mean time 99.42 (min = 64-max = 240), unkowm = 1. Neutropenia occurred during the 1st course of treatment in 9 cases, 2nd course in 6 cases, 3rd course in 3 cases, 4th course in 6 cases and in 1 case after the 5th, 8th and 10th courses of treatment (unknown = 9). Median time to resolution was 5 days (mean = 5.8 days). In 13 cases, Granulocyte-Colony Stimulating Factor was administered (unkown = 6). There were 5 cases in which

ocrelizumab was re-administered, without recurrence of neutropenia in 2 cases, with recurrence of neutropenia in 2 cases (unkown = 1).
Conclusion: This study shows that neutropenia during treatment with ocrelizumab can be profound, transient and with a long time to onset after the last injection. Late neutropenia has also been described with the 1st marketed anti-CD20, rituximab, and probably due to their long elimination half-life (around 20 days). Physicians need to be aware of this potential delayed risk.
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Depression Risk with Teriparatide: Disproportionality Analysis and Potential Mechanisms

Maxime MOINY[1], Jed HADJOUDJ[1], Zoubir DJERADA[2], Brahim AZZOUZ[1]

[1]Regional Centre Of Pharmacovigilance, Reims University Hospital, Reims, France. [2]Department of Pharmacology and Toxicology, Reims University Hospital, Reims, France

Introduction: Teriparatide is a recombinant human parathyroid hormone analog used in severe osteoporosis (when patients present more than 2 vertebral fractures). The drug is generally well tolerated. A case of depression associated with teriparatide use, reported to our Pharmacovigilance Department, prompted us to investigate this relationship. Although depression is listed in the teriparatide Product Information, the risk remains not well described. In this context, we investigated pharmacovigilance and literature data.
Aim/Objective: To describe the risk of depression with teriparatide.
Methods: We described reports of depression occuring with teriparatide and registered in the French national Pharmacovigilance Database (data from the inception of the database to February 29, 2024). Additionaly, we performed a case/non-case study. "Cases" were identified using the MedDRA High Level Group Term "Depressed mood disorders and disturbances". To demonstrate disproportionality, the Reporting Odds Ratio (ROR) and its 95% Confidence Interval (95% CI) were calculated. We also conducted a literature review to discuss potential underlying mechanisms.
Results: Of the 1,122,283 reports available in the French national Pharmacovigilance Database, 353 concerned teriparatide. A total of 12 reports of depression after teriparatide exposure were identified. The mean age of patients was 67 years (range 53 - 85 years) and 75% were women. Only 2 patients had a history of depression. Fifty per cent of the reports were considered serious. Six patients had suicidal ideations and 2 patients attempted suicide. The median time ton onset was 113 days but the median value was 30 days. Teriparatide was discontinuated in 9/12 reports and the outcome was favorable in most reports. The ROR of depression with teriparatide was 3.55 (95% CI 2.00-6.31).
The literature review identified 2 main mechanims: i) a direct mechanism via an effect on the PTH-2 brain receptor [1, 2] and ii) an indirect mechanism via disruption of calcium homesostasis [2, 3].
Conclusion: Depression risk after teriparatide exposure is largely unknown to the medical communauty. We have highlited a safety signal using pharmacovigilance data. Prescribers should be informed about this risk. Psychological support should be suggested to patients who require it. Symptoms occur mainly during the first months of treatment. Further studies are needed to explore the pathophysiologic mechanism.
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Institutionalizing a Digital System for Active Tuberculosis Drug Safety Monitoring in the Philippines

Shiferaw Gashaw[1], Chesa Desano[1], Balani Janille Cassiana[1], Cabasis Patrice[1], Rakuomi Viviani[2], Kate Kikule[3], do valle bastos luis Gustavo[3], Jaguga Collins[2], Kim Hoppenworth[3], Elizabeth Teketel[4], Sarah Millena Manga[5], Rein Carlo Fernandez[5]

[1]USAID MTaPS, MANILA, Philippines. [2]USAID MTaPS, Nairobi, Kenya. [3]USAID MTaPS, VA Arlington, USA. [4]USAID MTaPS, Addis Ababa, Ethiopia. [5]DOH Pharmaceutical division., MANILA, Philippines

Introduction: With the introduction of novel tuberculosis (TB) treatments like bedaquiline in the Philippines, active TB drug safety monitoring and management (aDSM) became imperative, as recommended by the World Health Organization (WHO).[1, 2] The Philippines Department of Health (DOH) initiated aDSM in 2015, piloting it in 10 healthcare facilities before expanding nationwide in 2016. However, the substantial increase in data volume from all Programmatic Management on Drug Resistance Tuberculosis (PMDT) sites posed challenges in data management. Manual data collection and causality assessment via email and Excel® were burdensome for healthcare workers (HCWs) and complicated data storage and maintenance.
Aim/Objective: To address the challenges encountered, the United States Agency for International Development (USAID) funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program worked with DOH to introduce a web-based Pharmacovigilance Monitoring System (PViMS) in 2016 and also expand and institutionalize the use of PViMS to all PMDT sites for effective aDSM to safeguard patients.
Methods: From 2019, The USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) program facilitated various interventions, including updating and issuing aDSM policies to provide clear guidance on implementation. Additionally, the program conducted training sessions for HCWs at all PMDT sites and provided supportive supervision. MTaPS also engaged stakeholders at all levels, including the DOH Disease Prevention and Control Bureau, Pharmacy Department, and the Food and Drug Administration, to support adoption, expansion, and sustainability. Furthermore, MTaPS enhanced the functionalities of PViMS to enable the implementation of active surveillance activities and linked it to VigiFlow for streamlined reporting to the Uppsala Monitoring Centre.
Results: Three aDSM policy documents were issued by DOH to facilitate implementation of PViMS at PMDT sites providing guidance on reporting. Since 2021, PViMS coverage expanded to all 199 PMDT sites, with 597 adverse events reported and causality assessments conducted. The utilization of PViMS data empowered HCWs to effectively address adverse events, ensuring patient safety and treatment adherence for improved health outcomes. Furthermore, the integration of PViMS with VigiFlow streamlined reporting processes, allowing seamless data sharing with the Uppsala Monitoring Center. Overall, these results demonstrated the successful implementation and impact of PViMS in enhancing PV and safety monitoring efforts in TB treatment programs across the Philippines.
Conclusion: PViMS significantly improved aDSM in TB treatment programs in the Philippines, showcasing its pivotal role in patient

safety monitoring efforts, backed by policy support, HCWs training, stakeholder engagement, and continuous system enhancements.

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Improving Awareness on Pharmacovigilance Reporting in Kenya

Clarice Ambale, Dorothy Aywak

Hospital Pharmacists Association of Kenya (HOPAK), Nairobi, Kenya

Introduction: Pharmacovigilance plays an important role in ensuring the safety of patients with the use medicines, medical devices and other health technologies. Having robust patient safety systems helps minimize incidence and impact of adverse events as well as maximize recovery from the same. Enhancing pharmacovigilance reporting enables learning from the captured incidents which when analyzed provide vital information for safety improvement (1, 2).

In Kenya, the Pharmacovigilance Electronic Reporting System (PvERS) is used for submitting reports the national regulatory authority by the general public, health care workers and market authorization holders.

Aim/Objective: The primary goal of the project was to enhance pharmacovigilance reporting, improve the quality of reports, and boost cadre-specific adverse event reporting in designated low-reporting counties in Kenya.

Methods: The Hospital Pharmacists Association of Kenya (HOPAK) identified a group of pharmacovigilance experts who possess a strong background in curriculum development and the creation and implementation of pharmacovigilance programs within the country. These experts came together to formulate a Continuing Professional Development (CPD) program tailored to the specific needs of each professional group.

The National Regulatory Authority- Pharmacy and Poisons Board Kenya core curriculum on Pharmacovigilance was adapted to suit the unique requirements of different target audiences and allocated time slots. To enhance the delivery of the program, two videos were created and incorporated into the training content. These videos served to illustrate adverse events and the prevalence of substandard medicines, aiding participants in grasping these concepts more effectively. The training content was validated through a one-day training.

Identification of the target audience was based on cadres and counties with low reporting rates. Staff from public, private, and faith-based facilities were included in the training to expand sensitization to different levels of facilities.

Results: Seven pharmacovigilance experts were engaged and developed the curriculum for the training. The training sessions were delivered through physical and virtual sessions over nine months starting from August 2023 to April 2024. The training targeted various cadres of healthcare workers including medical officers, nurses, clinical officers, and laboratory technologists among others. A total of 10 virtual and hybrid sessions and 4 one-day physical sessions were delivered. 1542 participants attended the virtual sessions while 148 participants attended the physical sessions. A total of 384 new accounts in the PVERS were created by trainees.

Conclusion: The training sessions achieved the desired output of increasing the number of healthcare workers with knowledge of pharmacovigilance and accounts with the pharmacovigilance reporting system. Continuous monitoring of the outcomes and impact of the project through an increase in the number and quality of reports would be done through follow-up of pharmacovigilance champions.

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Strengthening the Adverse Events Following Immunization Surveillance System for COVID-19 Vaccine Safety Monitoring and beyond: a case of Tanzania

Damas Matiko[1], Adam Fimbo[1], Lusaya Edgar[2], Betty AM[3], Simba Stephano[2], Luchytsky A[2], kate kikule[4], Kisera Nereah[5], Elizabeth Teketel[6]

[1]Tanzanian Medicine and Medical Device Authority, Dar es Salaam, Tanzania, United Republic of. [2]USAI MTaPS, Dar es Salaam, Tanzania, United Republic of. [3]Muhimbili University of Health and Allied Sciences (MUHAS),, Dar es Salaam, Tanzania, United Republic of. [4]USAI MTaPS, VA Arlington, USA. [5]USAI MTaPS, Nairobi, Kenya. [6]USAI MTaPS, Addis Ababa, Ethiopia

Introduction: Improved public health and well-being is one of the utmost important millennia goals. Tanzania health system involves both treatment and preventive measures, Immunization is one of the preventive health services provided. Since August 2021 to date. Tanzania has been implementing a vaccination campaign to protect its citizens against COVID-19 with five different vaccines, having administered more than 39 million doses by July 2023 [1]. Mass immunization at this scale makes vaccine safety monitoring particularly important to ensure trust, guarantee safety and mitigate potential adverse events.

Aim/Objective: The project aimed to explore and address the significant underreporting of adverse events post-COVID-19 immunization by healthcare workers, despite existing AEFI guidelines, compromising TMDA's ability to monitor, analyze, and respond to AEFI, and thereby jeopardizing public safety and the vaccination campaign's effectiveness.

Methods: From August 2022 to July 2023, the MTaPS Program through the USAID fund supported TMDA in strengthening the local capacity for vaccine safety monitoring. This was done through enhanced stakeholders' engagement, and alignment of technical materials with the current international guidance[2,3,4,]; development and use of training materials on COVID-19 vaccines pharmacovigilance, development of standard operating procedures (SOPs) and job aids for the Vigiflow database and it's decentralization to the regional level; training of trainers at zonal level (94) and healthcare workers(928) at facilities level; dissemination of COVID-19 vaccine safety information and Information Education Communication /IEC materials in form of hardcopies, audio, and video clips; and development and use of COVID-19 vaccine pharmacovigilance supportive supervision tools, to operationalize the system.

Results: Performance improvement at health facilities and regional levels led to better immunization service delivery, increased AEFI awareness and reporting for COVID-19 vaccines, and improved AEFI and ADR reporting across other vaccines and medications. This significantly impacted the country's reporting rates, whereby the number of regions reporting AEFI increased from 4 to 13 and 887 COVID-19 AEFIs. For other vaccines and medicines AEFI and ADRs increased

from 43 to 1571 and 254 to 1410, respectively. Regulatory responses to serious AEFIs were provided as feedback to healthcare workers, enhanced supervision, and improved facility readiness with AEFI kits.
Conclusion: The technical assistance provided has been instrumental in increasing the capacity of Tanzania to monitor vaccine safety, including that of COVID-19 vaccines. To further strengthen the system, we recommend refresher training, regular supportive supervision, continuous awareness-raising for AEFI reporting, and the widespread use of electronic reporting.

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An Approach to the Risk-Benefit Evaluation of Antivenoms Based on Bothrops Bites Cases from Digital Records

Guillermo Alberto Keller[1,2], Guillermo Temprano[1], Lorena Romano[1], Claudio Bonel[1], Adolfo Rafael de Roodt[1], José Christian Dokmetjian[1]

[1]Instituto Nacional de Producción de Biológicos {ANLIS Malbrán), Ciudad Autónoma de Buenos Aires, Argentina. [2]Universidad de Buenos Aires, Facultad de Medicina, Centro de Vigilancia y Seguridad de Medicamentos, Ciudad Autónoma de Buenos Aires, Argentina

Introduction: Accidents linked to Bothrops bites are pathologies of medical importance in whose treatment antisera (F(ab')2 equine antivenoms) are used. These medications have been associated with a decrease in mortality; however, there are no measures to evaluate the relationship between benefits and adverse reactions (1).
Aim/Objective: to describe risk/benefit relationship in Bothrops antivenom treatment.
Methods: Illnesses linked to Bothrops accidents are mandatory reporting in our country. All cases are uploaded to an integrated national Argentine health information system, along with data linked to the characteristics of the event, health history, treatment performed, evolution, and outcome. The data were analyzed, maintaining the anonymity of the patients and compared with the case list of adverse reactions received at the Antisera-production center. The frequency and relative risk linked to the events were analyzed using Statistica.
Results: 3,458 cases of accidents linked to Bothrops bites were identified. 2388 received antivenom, of which 2386 (99.9%) survived, and 2 (0.1%) died. The remaining 1070 patients did not receive antivenom, of which 2 (0.2%) died, while 1068 (99.8%) survived. The absolute risk reduction of mortality linked to antivenin administration was 0.00103 (NNT 969). The analysis of adverse reactions showed that they occur in 7.05% of patients (NNH 14), with 11% being serious reactions (NNH 129). Although no adverse reactions were fatal (and then disproportionate events were compared), a risk-benefit ratio by NNH/NNT ratio of 0.13 (for serious adverse reactions) and 0.01 (for adverse reactions in general) can be established.
Conclusion: Although the NNH/NNT coefficient shows a relationship that can be interpreted as not favorable (<1), it constitutes an example of evaluating events disproportionate in magnitude (Benefit: avoidance of death/Harm: completely reversible reactions). These data show the importance of developing a profit-weighted ratio, although it does not rule out that the calculated NNH/NNT value could be used for a historical comparison of the same product or with similar products as an additional quality parameter.

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Level of Knowledge about Pharmacovigilance in Undergraduate Students of Medicine and Pharmacy in Lima-Peru

Cecilia Beltrán-Noblega[1], Gladys Martha Delgado-Pérez[2]

[1]National Center for Pharmacovigilance and Technovigilance – General Direction of Medicines, supplies and Drug (DIGEMID), Lima, Peru. [2]Universidad Nacional Mayor de San Marcos, Lima, Peru

Introduction: The challenge of pharmacovigilance for health professionals in the world lies in communicating adverse effects or new potential risks to their national pharmacovigilance centers. [1]
The WHO, in the manual of indicators for pharmacovigilance systems, mentions that pharmacovigilance should be included in the curriculum of health careers such as medicine, pharmacy, among others, in each country. [2]

There have been several publications, where the level of knowledge in pharmacovigilance in medical and pharmacy students, is significant with gender, origin, faculty, knowledge of adverse reaction definitions. among others. [3-5]
Aim/Objective: To determine the association of medicine and pharmacy students and the level of knowledge on pharmacovigilance in Lima-Peru.
Methods: Observational, analytical, correlational cross-sectional design study. The sampling was by convenience, the sample was obtained during the 2019, 2020 and 2022 years, in a hybrid way, the face-to-face mode was through the coordinators of the universities and hospitals, and virtual through the coordinators student, 220 students of the last year of pharmacy and medicine, from public and private universities of Lima-Peru, who were administered a survey. The survey was validated with the participation of five experts in pharmacovigilance, using the expert judgment method (0.99 V of Aiken). The data were processed using the STATA program version 17.0 for Windows Vista. It was determined through the Chi2 statistical test with a significance $p<0.05$ value. Age and its level of association with the level of knowledge was established through Student's t-test. The study was approved by the UNMSM Ethics Committee with code 0116.
Results: 220 students participated, 141 (64.1%) from pharmacy and 79 (35.9%) from medicine, between public 50% and private 50% universities. They have higher level of knowledge about pharmacovigilance students: from pharmacy $p = 0.0001$, from private universities $p = 0.0032$, female sex $p = 0.044$, finally it was obtained that 50% were up to 26 years old with IQ of 6 years (Mean 27.3±5.6, $p = 0.001$), meaning that the older the age the higher the knowledge was.
Conclusion: The variables sex, age, faculty, and type of university turned out to be significantly associated with the level of pharmacovigilance knowledge ($p<0.05$).

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Impact of stringent vigilance systems for medical devices and Invitro diagnostics in Africa: A case study in Tanzania

Christian Kapinga

Tanzania Medicines and Medical Devices Authority, Dodoma, Tanzania, United Republic of

Introduction: The Tanzania Medicines and Medical Devices Authority (TMDA) started regulation of medical devices in 2008 and eventually regulation of invitro diagnostics by 2015, the Authority is currently implementing all regulatory functions which include market authorization, importation and exportation control, manufacturing site inspection, post marketing surveillance as well as vigilance of the respective products. The latter involves the established systems for reporting, collection as well as assessment of adverse events and adverse incidents pertaining use of medical devices and invitro diagnostics by manufactures, importers and distributors, healthcare workers and end consumers.
Aim/Objective: The Aim of this study was to see how mandatory reporting of adverse events has impacted the public health
Methods: This retrospective observation study conducted to see the impact of established stringent and mandatory reporting systems for adverse events and incidents occurring from the use of medical devices and invitro diagnostics in Tanzania. The idea was to conduct a critical analysis of the adverse events and incidents collected by the Authority through different established ways of collecting them since 2019 as evidenced from the register available. The study will also focus distribution of the types of devices mostly reported, manufacturing countries of the respective devices, the factors affecting reporting of these events as well as regulatory decisions taken which had impact on the public health.
Results: From year 2019-to February, 2024 the Authority received and collected a total of 39, 98, 22, 143, 247 and 123 of adverse events and incidents respectively, the trend indicates a significant increase in the numbers which have been contributed by the deliberate efforts of the Authority through sensitization programmes as well as inspection activities. Also, the regulatory decision taken through the events reported might have contributed to the willingness and passive reporting from the stakeholders.
Conclusion: Establishment of the intact vigilance system is crucial as far as medical devices and invitro diagnostics is concerned, the regulation these products is still lagging behind in the African continent, the NRA should consider its implementation as the impact is huge to the public health.
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Sulfamethoxazole-Trimethoprim and Risk of Blood Disorders: An Active Comparator Restricted Disproportionality Analysis

Rebecca Preyra[1], Niaz Chalabianloo[2], Flory Muanda[1,3,4,2]

[1]Department of Physiology and Pharmacology, Western University, London, Canada. [2]Department of Epidemiology and Biostatistics, Western University, London, Canada. [3]ICES Western, London, Canada. [4]Lawson Health Research Institute, London, Canada

Introduction: While Sulfamethoxazole-trimethoprim (SMX-TMP) is commonly prescribed for skin, urinary tract, respiratory tract, and gastrointestinal tract infections, research on its potential association with pancytopenia, aplastic anemia, neutropenia, and thrombocytopenia is limited.[1]
Aim/Objective: To conduct an active comparator restricted disproportionality analysis using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database to detect signals of potential associations between SMX-TMP use and pancytopenia, thrombocytopenia, neutropenia, and aplastic anemia.
Methods: We analyzed adverse drug events (ADEs) reported in the FAERS databases from 2004Q1 to 2023Q4, using the Medical Dictionary for Regulatory Activities (MedDRA)-v24 preferred term to identify adverse events (AEs), such as pancytopenia, aplastic anemia, neutropenia, and thrombocytopenia. The study drugs included SMX-TMP and comparator drugs azithromycin, amoxicillin/clavulanic acid, and nitrofurantoin. To detect signals, we utilized reporting odds ratios (ROR) to compare the proportion of pancytopenia, aplastic anemia, neutropenia, and thrombocytopenia reports for SMX-TMP to the comparator drugs. All analyses were restricted to ADEs considered the primary suspects in the database.
Results: Our results showed a higher proportion of reports for pancytopenia (199 cases of 10,069 [1.98%] vs. 43 cases of 21,435 [0.20%]; ROR, 10.03 [95% CI, 7.20 to 13.96]), aplastic anemia (12 cases of 10,069 [0.12%] vs. 7 cases of 21,435 [0.03%]; ROR, 3.65 [95% CI, 1.44 to 9.28]), neutropenia (159 cases of 10,069 [1.58%] vs. 55 cases of 21,435 [0.26%]; ROR, 6.23 [95% CI, 4.59 to 8.48]), and thrombocytopenia (279 cases of 10,069 [2.77%] vs. 154 cases of 21,435 [0.72%]; ROR, 3.94 [95% CI, 3.23 to 4.80]) for SMX-TMP compared to azithromycin. Similar signals were observed with amoxicillin/clavulanic acid and nitrofurantoin.
Conclusion: SMX-TMP may be associated with a higher risk of blood disorders. These findings require further investigation with pharmacoepidemiologic studies.
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Safety of Sulfamethoxazole-trimethoprim for the Treatment of Bacterial Infection in Outpatient Settings: A Meta-analysis and Pharmacovigilance Study

Rebecca Preyra[1], Lujain Ez eddin[1], Fatemeh Ahmadi[1], Atefeh Jafari[1], Niaz Chalabianloo[2], Flory Muanda[1,3,4,2]

[1]Department of Physiology and Pharmacology, Western University, London, Canada. [2]Department of Epidemiology and Biostatistics, Western University, London, Canada. [3]ICES Western, London, Canada. [4]Lawson Health Research Institute, London Health Sciences Centre, London, Canada

Introduction: While sulfamethoxazole-trimethoprim (SMX-TMP) is commonly used to treat urinary tract, skin, and respiratory tract infections in adult outpatients,[1] its safety profile in this setting has not been fully studied.
Aim/Objective: To summarize existing evidence on SMX-TMP's safety in outpatient settings, identify areas for further investigation, and conduct a pharmacovigilance study to confirm previous signals and identify new ones using FDA Adverse Event Reporting System (FAERS) databases.
Methods: A systematic review was conducted using the MEDLINE and Embase databases up to October 13, 2023, to identify and synthesize the findings of studies comparing SMX-TMP with other antibiotics that share a similar indication. Meta-analysis was performed where applicable. An active comparator restricted disproportionality analysis study of the FAERS Database was conducted from 2004Q1 to 2023Q4 to confirm prior signals and investigate understudied signals using reporting odds ratios (ROR) to detect potential signals. A Medical Dictionary for Regulatory Activities (MedDRA)-v24 preferred term was used to identify adverse events (AEs) including rash, Steven Johnsons Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).
Results: 53 studies were identified. SMX-TMP was associated with a 2.6-fold increased risk of rash compared to other antibiotics (RR 2.6, 95% CI [1.7-3.9], 24 RCTs, I^2 = 0%). Results were consistent in subgroup analysis. Our pharmacovigilance study showed that compared to azithromycin, SMX-TMP had significantly higher reports for AEs: a 2.9-fold increase in rash (15.8% vs. 6.1%; ROR, 2.89 [95% CI 2.68-3.13]), a 5-fold increase in SJS (4.6% vs. 0.93%; ROR, 5.06 [95% CI 4.28-5.98]), a 3-fold increase in TEN (2.0% vs. 0.59%; ROR, 3.44 [95% CI 2.75-4.29]), and a 10-fold increase in DRESS (4.08% vs. 0.42%; ROR, 10.21 [95% CI 8.11-12.85]).
Conclusion: SMX-TMP may carry a higher risk of rash, particularly severe skin reactions, than other antibiotics. However, further pharmacoepidemiological studies are needed to confirm these findings.
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Monitoring the Effects of the COVID-19 Pandemic on Antidepressant Utilization Trends in Iran

Fatemeh Soleymani, Forouzan Taheri, Ali Rahmani

Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of

Introduction: After the announcement of the COVID-19 pandemic and its consequences such as social restrictions and lockdowns a surge in mental disorder symptoms was observed globally with depression and anxiety among the highest ones. (1,2) In Iran with pieces of evidence showing a great deal of self-medication, the rational use of antidepressants has always been a matter of concern.
Aim/Objective: This study was conducted to analyze the pattern of antidepressant prescription and utilization after the pandemic.
Methods: A cross-sectional study was designed. Five years of prescription claims data and sales data were collected from Iranian insurance agencies and the national regulatory authority's databank respectively to find out the changes in the pattern of antidepressant consumption and prescription in the Iranian population. All data were reported as DDD/1000 inhabitants/day (DID).
Results: Over 800 million prescriptions were collected in this study The amount of prescribed antidepressants, increased from 4.68 in 2016 to 7.20 in 2021. The sales amount, encompassing both prescriptions and self-medication, increased from 33.3 DDD/1000 inhabitants/day in 2016 to 50.2 DDD/1000 inhabitants/day in 2021. The data shows that the highest increase in prescribed antidepressants was observed with SSRIs (N06AB), which rose from 3.87 in 2016 to 6.14 in 2021.
Conclusion: Due to the COVID-19 pandemic, there has been a notable surge in the dispensing of antidepressant medications to the general population in Iran. This has raised concerns among health policymakers regarding the overuse and irrational prescription of these medicines. It is imperative to develop strategies not only to revert the pattern to its pre-pandemic state but also to promote the rational use of these medications. Furthermore, conducting additional studies may aid in the development of preventive strategies to address similar global pandemic situations.
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Medication Errors Reporting by Nurses Through Electronic Reporting System, a Realist Review

Gloria Shalviri[1,2], Bahareh Yazdizadeh[2], Reza Majdzadeh[3], Fariba Mirbaha[2], Kheirollah Gholami[1]

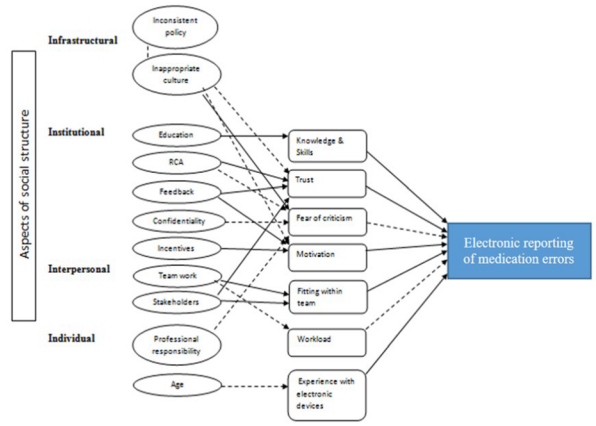
[1]Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of. [2]Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of. [3]School of Health and Social Care, University of Essex., Essex, United Kingdom

Introduction: Adverse drug events are recognized as a major cause of death in the world. Electronic system for reporting medication errors (MEs), is one of the applied interventions to improve medication safety [1]. However, this intervention has not been reviewed realistically to identify and explain the interaction between context, mechanism and outcome; and to reveal how improving context might lead to better implementation of the intervention.
Aim/Objective: To identify the "mechanisms" that have a positive or negative effect on electronically reporting of MEs by nurses. To detect important "areas" that determine reporting by different mechanisms. To formulate a program theory for MEs electronic reporting system.
Methods: We searched two databases (Medline and Embase) and references of included articles to extract evidence related to MEs reporting by nurses through electronic reporting system. All study designs and outcomes were considered. We extracted Context-Mechanism_Outcome Configuration (CMOC) among selected

manuscripts. Extracted evidence was collected and analyzed through the approach derived from the realist review theory. This review was done systematically and explained how, why and in what contexts this intervention works. Negative effects were also investigated. To compile final program theory, we included the suggestions of the stakeholders.

Results: Among 1907 extracted articles, 19 papers met our inclusion criteria. By reviewing the eligible articles, a total of 22 CMOCs were extracted. The main extracted social and professional components, as well as the components affecting the use of technology, included the following: team-working to report MEs, lack of time, fear of criticism, incentive systems for reporting, and easy use of the reporting tool. Based on extracted CMOCs, we identified that the program theory regarding the electronic reporting of MEs by nurses are based on two main categories: the impact of social factors (Fig 1), as well as the effect of acceptance and use of technology, on the decision to report MEs. There are complex relationships between the contexts in which nurses work, such as hierarchical relationships, and followings: strong norms regarding the reporting of MEs, roles and responsibilities with less clarity, how to apply knowledge in practice, fear of criticism, personal responsibility, need to manage reputation and position in the team.

Fig 1. Program theory for electronic reporting of MEs. (Smooth and dotted arrows represent positive and negative influence, respectively)



Conclusion: This realistic review reveals the importance of the context in which the intervention of electronical ME reporting is implemented and the attempt to explain how and why the intervention works in different contexts. Our findings show that nurses do not report MEs just due to the lack of knowledge, but the impossibility of applying their knowledge to practice is also a fundamental problem. It is necessary to identify the mental and social norms of nurses and apply them to the design of interventions.

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The Current Pharmacovigilance System in Timor-Leste by an Indicator-Based Assessment Tool

Juanina da Costa[1,2], Pramote Tragulpiankit[2], Wichit Nosoongnoen[2], Watcharee Rungapiromnan[3]

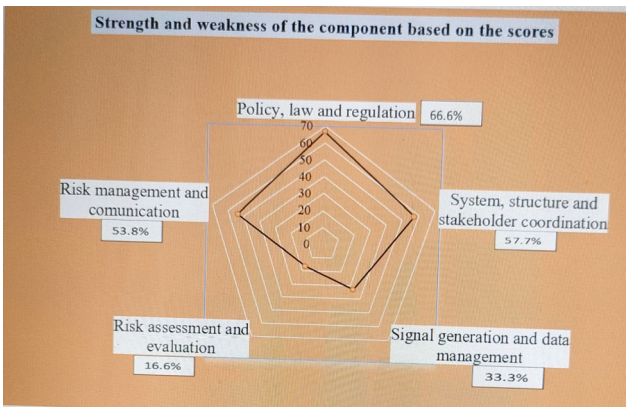
[1]National Hospital Guido Valadares, Dili, Timor-Leste. [2]Faculty of Pharmacy, Mahidol University, Bangkok, Thailand. [3]Health Product Vigilance Center, Thai Food and Drug Administration Ministry of Public Health, Bangkok, Thailand

Introduction: Pharmacovigilance (PV) is a continuous process that involves monitoring a drug's safety after it has been approved and put on the market (1). Timor-Leste (TL) is a young country that gained independence from Indonesia 25 years ago (2). TL introduced a PV program in 2016 and has had the status of an associate member of international drug monitoring since 2019 (3).

Aim/Objective: This study aims to investigate and provide an overview of the current situation of the PV system in TL.

Methods: A documentary review and face-to-face discussion with the pharmacovigilance staff were conducted at the National Pharmacovigilance Center among March 2024. The pharmacovigilance system was reviewed based on five components using the assessment-based pharmacovigilance assessment tool. The tool consists of 43 indicators (26 core and 17 complementary indicators). Each indicator fulfilling the criteria was given a score of 2 for the core indicator and 1 for the supplementary score. Each component's total sum of scores was calculated and expressed in percentages.

Results:



The interview was conducted face-to-face with Dr. Celeste Fernandes Xavier Cham, head of the Pharmacovigilance Department, National Directorate of Pharmacy and Medicine. and Dr. Cesaltino da Silva Belo, responsible for the Pharmacovigilance Center for adverse drug reaction reporting. The results are shown in Figure 1.

Conclusion: The study found that PV activity was legally supported by the Decree-Law-Nu 21/2015, Ministerial Diploma-Nu 18/2015, and 41/2020; organic functional structure of the general directorate of health, article 40-part j on the implementation of its activity. However, four components indicate that the PV process was poorly implemented. ADR reporting is part of risk assessment and evaluation involving patient safety, which is a major concern for healthcare professionals.

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The Characteristics of Individual Case Safety Reports (ICSRs) in Timor-Leste

Juanina da Costa[1,2], Pramote Tragulpiankit[2], Wichit Nosoongnoen[2], Watcharee Rungapiromnan[3]

[1]*National Referral Hospital Guido Valadares, Dili, Timor-Leste.* [2]*Faculty of Pharmacy, Mahidol University, Bangkok, Thailand.* [3]*Health Product Vigilance Center, Thai Food and Drug Administration Ministry of Public Health, Bangkok, Thailand*

Introduction: The pharmacovigilance system in Timor-Leste was established in 2016 after the development of the Medicines Act of 2010 and later became an associate member of the WHO Programme for International Drug Monitoring in 2019 (1, 2). The National Pharmacovigilance Center (NPC) has a major role to play in the promotion of healthcare professionals for spontaneous reporting of adverse drug reactions or individual case safety reports (ICSRs).
Aim/Objective: To determine the number and characteristics of ICSRs of NPC in Timor-Leste.
Methods: The retrospective ICSRs between the established years, i.e., 2016 to March 2024, were descriptively analyzed by SPSS version 25. The characteristics of reports were described based on the demographic distribution of the patients, the sources of reports, and the suspected drug classification by the Anatomical Therapeutic Chemical (ATC) classification code. System organs were classified according to the criteria of the Council for International Organizations of Medical Science (CIOMS). The severity and outcomes of patients were categorized.
Results: A total of nine ICSRs were reported to the NPC. Seven (77.8%) were male patients. Ages between 40-75 years old were reported by 77.8%. All of them were reported by clinical doctors. Five (55.5%) were suspected of being anti-infective for system use, and four (44.4%) and three (33.3%) suffered adverse effects from skin disorders and gastrointestinal disorders, respectively. Eight (88.8%) were identified as serious adverse events. From these, life-threatening was seven (77.7%) and caused prolonged hospitalization was two events (22.2%).
Conclusion: Although the number of ICSRs in Timor-Leste is relatively low and underreporting needs improvement of the pharmacovigilance system, anti-infective for systemic use and skin disorders were major drug groups, as were organ-affected disorders, which consisted of other spontaneous reporting patterns among other countries.
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Technological Tools and Guidelines in Medication Name Screening: SFDA's Approach and Outcomes

Ghadeer Banasser, Abdulaziz Al Draihm

Saudi Food and Drug Authority (SFDA), Riyadh, Saudi Arabia

Introduction: Medication errors pose a significant risk to patient safety, necessitating effective strategies for mitigation. The Saudi Food and Drug Authority's (SFDA) Drug Sector has developed comprehensive guidelines, titled "Guidance for Naming of Medicinal Products," to aid pharmaceutical companies in selecting appropriate invented names. These guidelines aim to reduce medication errors by considering factors such as name similarities, use of International Nonproprietary Names (INN) or United States Adopted Names (USAN) stems, and utilization of misleading or promotional assertions. Furthermore, the guidelines discourage the inclusion of product-specific attributes, manufacturer names in certain ways, and certain qualifiers in invented names.
Aim/Objective: The main objective of this study is to assess the effectiveness of the SFDA's guidelines and screening methods for medication names, with a specific focus on evaluating the tools and technological resources employed in the screening process for identifying name similarity.
Methods: The appropriateness of the proposed invented names is evaluated through a rigorous screening process. Advanced tools are employed to thoroughly assess name similarity. The screening mechanisms utilized encompass the Saudi Name Registration (SNR), Phonetic and Orthographic Computer Analysis (POCA), Micromedex, Medicines Complete, UpToDate Lexidrug (formerly Lexicomp), and the newly introduced WHODrug Insight. WHODrug Insight leverages global data obtained from the Uppsala Monitoring Centre (UMC) database to identify identical and similar names on a global scale.
Results: In 2021, a total of 421 proposed invented names were subjected to evaluation. Approximately one-third of the proposed names (121 out of 421, accounting for 29%) were rejected. Name similarity emerged as the primary reason for rejection, constituting 47.7% of the cases. The evaluation process at the SFDA relied on advanced tools, and WHODrug Insight proved particularly valuable in identifying global name conflicts.
Conclusion: The SFDA's guidelines and technologically-driven name screening process effectively identify name appropriateness and similarities and have the potential to mitigate medication errors. Rigorous evaluation, including comprehensive name similarity analysis, plays a crucial role in rejecting inappropriate names. The study emphasizes the importance of disseminating and implementing this screening process globally among all regulatory bodies. Such implementation would yield positive outcomes in promoting the safe utilization of medications, particularly in mitigating medication name confusions.
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Improving Medication Safety in Saudi Healthcare System: The Role of Regional Pharmacovigilance Officers (RPVOs) in Implementing Additional Risk Minimization Measures

Aseel Alshayji, Naser Aljaser, Fawaz Alharbi

SFDA, Riyadh, Saudi Arabia

Introduction: The Saudi Food and Drug Authority (SFDA) plays a critical role in implementing Additional Risk Minimization Measures (aRMMs) for medications in Saudi Arabia. To promote medication safety, the SFDA "Established 25 regional pharmacovigilance centers in different areas in Saudi Arabia. The purpose of establishing these centers is to improve the reporting culture of side effects to reduce the risks associated with using medications and improve medication safety in Saudi Arabia.

Aim/Objective: Our initiative in cooperating with Regional Pharmacovigilance Officers (RPVOs) aims to improve the distribution and availability of aRMMs in local hospitals. Also, we aim to raise awareness about approved aRMMs, improve the aRMMs implementation, and communicate with Healthcare Professionals (HCPs).
Methods: At the beginning of 2023, the SFDA met with RPVOs to explain to them the initiative's objectives. We have established three Key Performance Indicators: ensuring access to approved aRMMs by HCPs in the hospital, ensuring the availability of approved aRMMs in the hospital, and conducting one-to-one educational visits to HCPs to increase their knowledge and improve implementation of aRMMs. Educational visits included pre- and post-visit surveys and discussions. The Corrective actions were carried out in accordance with the desired outcomes.
Results: The number of HCPs who received aRMMs experienced a significant rise, reaching 6,492 HCPs in 2023. This noteworthy increase can be attributed to the implementation of a monthly distribution system, wherein the approved ARMMs were transmitted electronically to the RPVOs via email. Upon evaluation, it was determined that the availability of aRMMs in hospitals stood at about 70%. To enhance this figure in the future, we have initiated a corrective plan that involves redistributing aRMMs within hospitals and establishing direct communication channels between the Qualified Person Responsible for Pharmacovigilance in a pharmaceutical company and RPVOs to address any issues of missing aRMMs promptly. Regarding educational visits, the RPVOs successfully conducted 100 visits to HCPs, surpassing the initial target by 100%. During these visits, HCPs found that aRMMs materials are useful and they expressed high satisfaction with the visits.
Conclusion: Our project enhances HCP awareness of approved aRMMs at local hospitals as well as their accessibility and availability. Furthermore, Educational visits have been effective in enhancing HCP understanding of aRMMs and they should be conducted more frequently. Further efforts are needed to improve the regular distribution of aRMMs by pharmaceutical companies.
References
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Adverse Events Associated with Sodium-Glucose Co-transporter-2 Inhibitors: A UK National Pharmacovigilance Study

Ahmed Hassan[1,2], David Ryan[1], Andrew Scourfield[1]

[1]*Clinical Pharmacology, University College London Hospital, London, United Kingdom.* [2]*School of Medicine, Cardiff University, Cardiff, United Kingdom*

Introduction: Approximately 1 million sodium-glucose cotransporter-2 inhibitors (SGLT2-i) are dispensed each month in England.[1] Whilst these drugs were originally developed to treat type 2 diabetes, they are now licensed for other indications including heart failure and chronic kidney disease.[2]
Large randomised clinical trials (RCTs) of SGLT-2i showed adverse drug reactions (ADRs) related to urinary and reproductive tract infections and euglycaemic diabetic ketoacidosis among others.[2] The wider indications and populations now eligible for SGLT2-i raise questions regarding the generalisability of this RCT safety data to real-world populations.[3] Therefore, robust pharmacovigilance is essential to capture real-world safety profiles accurately.
Aim/Objective: This study aims to compare UK pharmacovigilance data for SGLT-2i with signals from RCTs.
Methods: A retrospective analysis of the UK national pharmacovigilance database was conducted, analysing serious or fatal ADRs associated with SGLT2-i from January 2014–November 2022.[4] Disproportionality analysis using proportional reporting ratios (PRR) and 95% confidence intervals was employed to identify SGLT2-i ADRs. Statistically significant PRRs (adjusted for multiple testing with Bonferroni's correction) were grouped according to clinical relevance and compared to ADRs from RCTs to identify novel safety signals.
Results: There were 17,782 serious or fatal ADRs associated with SGLT2-i reported for 3,991 people. The mean age of people with an ADR was 55 years (standard deviation 12.8 years) and approximately half were female (1,782/3,991; 44.7%). The greatest number of reports related to dapagliflozin (9,344 reports; 53%), followed by empagliflozin (5,512; 31%) and canagliflozin (2,926; 16%). Reported ADRs were consistent with findings from RCTs with all SGLT2-i being associated with increased signals for diabetic complications, urinary and reproductive tract infections and acute kidney injury (Table 1). These signals were consistent across all SGLT2-i assessed, although empagliflozin appeared to be associated with higher reporting of metabolic ADRs compared to other SGLT2-i. There were novel signals identified for polycythaemia for dapagliflozin and empagliflozin but not canagliflozin (Table 1).

Table 1: Adverse drug reactions significantly associated with SGLT2-i from the UK national pharmacovigilance database.

ADR	Medication	Number of ADR reports	PRR (95% CI)
Diabetic ketoacidosis	Dapagliflozin	504	119.2 (108.5-131.0)
	Empagliflozin	528	227.8 (208.5-248.9)
	Canagliflozin	194	145.5 (127.2-166.5)
Euglycaemic diabetic ketoacidosis	Dapagliflozin	107	207.3 (164.6-261.0)
	Empagliflozin	146	623.4 (502.1-774.0)
	Canagliflozin	52	298.9 (223.4-400.0)
Urinary tract infection	Dapagliflozin	68	10.5 (8.3-13.4)
	Empagliflozin	36	9.9 (7.2-13.8)
	Canagliflozin	41	23.5 (17.4-31.9)
Fournier's gangrene	Dapagliflozin	58	226.8 (164.9-312.1)
	Empagliflozin	50	326.9 (234.9-454.8)
	Canagliflozin	16	167.1 (100.1-278.9)
Acute kidney injury	Dapagliflozin	53	2.5 (1.9-3.3)
	Empagliflozin	33	2.8 (2.0-4.0)
	Canagliflozin	22	3.9 (2.6-5.9)
Toe amputation	Dapagliflozin	9	92.4 (44.9-190.3)
	Empagliflozin	13	266.8 (141.7-502.3)
	Canagliflozin	16	744.1 (410.8-1348.0)
Balanoposthitis	Dapagliflozin	12	82.1 (44.2-152.5)
	Empagliflozin	12	147.7 (79.6-274.2)
	Canagliflozin	3	66.7 (21.0-211.7)
Diabetic foot	Dapagliflozin	7	89.8 (39.7-203.4)
	Empagliflozin	7	161.6 (71.4- 365.7)
	Canagliflozin	6	279.1 (117.2-664.7)
Genital candidiasis/ genital infection fungal	Dapagliflozin	7	479.1 (161.1-1425.0)
	Empagliflozin	5	461.7 (151.2-1410.2)
	Canagliflozin	3	354.2 (101.1-1241.2)
Polycythaemia	Dapagliflozin	3	10.3 (3.3-32.3)
	Empagliflozin	5	31.3 (12.8-76.5)
	Canagliflozin	nil	nil

ADR, adverse drug reaction; PRR, proportional reporting ratio; 95% CI: 95% confidence interval. The green colour represents known safety signals, and pink colour represents novel safety signals

Conclusion: Real-world ADRs for SGLT2-i were largely congruent with data from RCTs. The association with polycythaemia is supported by post-hoc analyses of RCTs, a potential impact of SGLT-i on erythropoiesis.[5] There is a paucity of data on intra-drug class metabolic safety of SGLT2-i, which warrants further study. Pharmacovigilance data may reveal novel ADR and intra-drug class safety signals, but caution must be applied due to reporting or misclassification bias in spontaneous ADR databases.
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Carpal Tunnel Syndrome and Immune Checkpoint Inhibitors: Review of French Pharmacovigilance Database and Literature

Caroline JOYAU[1], Elliot EWIG[2], Mélanie SAINT-JEAN[3], Anne-Laure CHENE[4], Marina BABIN[5], Gwenaëlle VEYRAC[6]

[1]Regional Pharmacovigilance Center of Nantes, Clinical Pharmacology Department, University Hospital of Nantes, Nantes, France. [2]Department of Pharmacology and Pharmacovigilance Center of Nice, University Hospital of Nice, Nice, France. [3]Department of Medical Oncology, ICO Cancer Center, Saint-Herblain, France. [4]Department of Pneumology, University Hospital of Nantes, Nantes, France. [5]Department of Pharmacology-Toxicology and Pharmacovigilance, University Hospital of Angers, Angers, France. [6]Regional Pharmacovigilance Center of Nantes, Clinical Pharmacology Departement, University Hospital of Nantes, Nantes, France

Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized treatment approaches and prognoses for several types of malignancies. They also lead to immune related adverse events (irAEs). Neurologic irAEs may be relatively less common than other irAEs. Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the general population. Several factors are associated with an increased risk of developing CTS, including genetic predisposition, professions with repetitive wrist movements, female gender, advanced age, obesity, hypothyroidism, diabetes.
Aim/Objective: To characterize CTS in patients treated with ICIs.
Methods: A search was conducted in the French Pharmacovigilance Database (FPD) and in PubMed with the following terms : "carpal tunnel syndrome", "nivolumab", "pembrolizumab", "cemiplimab", "dostarlimab", "atezolizumab", "avelumab", "durvalumab", "ipilimumab", "tremelimumab", "relatlimab" and "immune checkpoint inhibitors".
Results: In the FPD, we found 7 cases of CTS with ICIs. All patients were women (median age: 66 years; range: 45-77). The ICIs were pembrolizumab (n = 4) and nivolumab (n = 3). The indication was melanoma in 6 cases. The median time to onset was 6 months (range 1-12). Carpal tunnel syndrome was bilateral in 5 cases. Surgery or systemic corticosteroid therapy were the corrective treatments in most patients. The outcome was favorable in 6 cases and unknown in one. In the literature, we found 6 publications describing 19 cases of CTS with ICIs, in 10 women and 9 men (median age: 74 years; range: 40-97). The ICIs were pembrolizumab (n = 9), nivolumab (n = 7), ipilimumab/nivolumab (n = 1), atezolizumab (n = 1) and avelumab (n = 1). The indication was melanoma in 11 cases. The median time to onset was 3 months (range 1-24). Carpal tunnel syndrome was bilateral in 17 patients (89,5%). Corrective treatment was mostly surgery and/or systemic corticosteroid therapy and/or corticosteroid infiltration. The outcome was favorable in 15 cases (79%).
Conclusion: The significant relief and improvement of symptoms following treatment with steroids in some cases, along with the bilateral occurrence, strongly suggest that the symptoms are a result of a neurologic irAE rather than an independent coincidental event. The exact neurological irAE mechanism remains unclear, but hypotheses have been suggested (T cell dysregulation, inflammation of the vessels and perineural edema around the nerve). The association of CTS with ICIs is exceedingly rare.
Given the prevalence of CTS in the general population and extension of indications of ICIs, development of carpal tunnel syndrome during treatment with ICIs is likely underrecognized and underreported.

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A Feasibility Assessment of the FDA Adverse Event Reporting System for the Detection of Cannabis-Related Safety Signals

Priscilla Orechio de Morais Victor Lopes, Christopher A. Gravel, Cory S. Harris

University of Ottawa, Ottawa, Canada

Introduction: The FDA Adverse Event Reporting System (FAERS) is a well-established system for monitoring adverse drug reactions (ADR) related to pharmaceutical drugs [1] and can be used to detect unexpected emerging safety signals [2]. However, its applicability to cannabis safety surveillance remains unclear due to the drug's legal status varying worldwide [3] and whether the variables captured by existing spontaneous reporting systems are sufficient to identify cannabis-related safety signals. Moreover, the potency and composition of cannabis-derived products can vary widely, making it difficult to determine a direct correlation between adverse events and specific products [4].
Aim/Objective: To assess the feasibility of using FAERS for cannabis safety surveillance by characterizing cannabis reporting and exploring trends over time.
Methods: ADR reports were queried from 1999 through 2023. We explored self-reported terminology used to describe cannabis products and classified them into pharmacologically and pharmacovigilance-relevant groups [5, 6]. Additionally, we characterized the distribution of reporter demographic characteristics and the MedDRA [7] terminologies at the preferred term level in reports with cannabis.
Results: A total of 1204 unique terms were used to report cannabis-related products, of which 660 (54.8%) represented the major cannabinoids found in medical and recreational products. A total of 42654 reports were identified mentioning cannabis-derived products, with 14412 (33.8%) reported as primary suspect drugs and 9806 (23.0%) reported as secondary suspect drugs. We noted reporting trends reflective of the availability of marketed cannabis-derived drugs by country and the legalization status over time. We also

summarized the extent to which other reporting characteristics contributed to feasibility.

Conclusion: The cannabis post-marketing surveillance process poses unique challenges to meet the distinct characteristics of these products. In our descriptive analysis of cannabis reporting in FAERS, we found mixed results on the potential feasibility of using this spontaneous reporting system for a similar purpose as with pharmaceutical safety signal detection. This project highlights the uniqueness of cannabis-related adverse events, implying that, ultimately, additional aspects may also be considered when collecting, coding, and assessing self-reports of ADR regarding cannabis use.

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Hepatic Disorders Associated with GLP-1 Receptor Agonists: Analysis of individual case safety reports in VigiBase

Sarah Banholzer[1], Irene Scholz[2], Manuel Haschke[1], Thomas Stammschulte[2]

[1]Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern, Switzerland. [2]Swissmedic, Pharmacovigilance Unit, Bern, Switzerland

Introduction: Glucagon-like peptide-1 (GLP-1)-based therapies are used in the treatment of type 2 diabetes and obesity. The following GLP-1 receptor agonists are currently authorized: Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide and Tirzepatide (dual-acting GLP-1 receptor agonist and Glucose-Dependent Insulinotropic Polypeptide (GIP) agonist). According to Livertox (1) GLP-1 receptor agonists have not been associated with hepatic ADRs. However, the product summaries mention ADRs of the liver with Dulaglutide, Liraglutide and Semaglutide (2). Furthermore, some analyses have shown possible associations between GLP-1 receptor agonists and potential hepatic ADRs (3, 4) and several case reports have already been published on the subject (5-8).

Aim/Objective: To identify possible associations between GLP-1 receptor agonists and hepatic ADRs in individual case safety reports recorded in VigiBase.

Methods: The ICSRs reported for the GLP-1 receptor agonists and the standardized MedDRA query (SMQ) "hepatic disorders" (narrow search) were extracted from VigiBase as a de-duplicated dataset on 20 March 2024 (MedDRA version 26.1).

Results: A total of 2'875 ICSRs were identified, of which 955 (33.2%) related to exenatide, 792 (27.2%) to liraglutide, 528 (18.4%) to dulaglutide, 506 (17.6%) to semaglutide, 152 (5.3%) to tirzepatide and 15 (0.5%) to lixisenatide. 66.2% of these ICSRs were classified as serious. Approximately half of the hepatic disorders (54.3%) were reported by healthcare professionals. The most frequently reported reactions (preferred term (PT) number of ICSRs and percentage) were as follows: hepatic enzyme increased (394, 13.7%), hepatic steatosis (284, 9.9%), alanine aminotransferase increased (244, 8.5%) and liver disorder (193, 6.7%).

Conclusion: This analysis of global ICSRs provides possible evidence that some GLP-1 receptor agonists may be associated with hepatic side effects. However, it is not possible to assess a causal relationship within this analysis. In light of the increasing global use of GLP-1 receptor agonists, further pharmacovigilance activities and studies are needed to confirm these findings and to describe these potential reactions in more detail.

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Classification and Evaluation of Pre-Authorized Pharmacovigilance Agreements of Advanced Therapy Medicinal Products Related Marketing Authorization Holders (MAHs): An Observational Study

Amal Arafah, Abdullatif AlOtaibi, Hammad Aldali, Hamad Alnomay

Saudi FDA, Riyadh, Saudi Arabia

Introduction: The adoption of personalized therapies in medicinal production, as outlined by the SFDA, presents both opportunities and challenges in the realm of pharmacovigilance. The aim is to enhance patient safety and gain a better understanding of treatment outcomes. This involves various activities such as monitoring the safety and effectiveness of advanced therapy medicinal products, conducting long-term follow-up, conducting personalized risk-benefit

assessments, generating real-world evidence, and ensuring compliance with regulatory standards. The most recent update to the Saudi Good Pharmacovigilance Practices mandating Marketing Authorization Holders to establish pre-authorized pharmacovigilance agreements between relevant parties to ensure the proper implementation of pharmacovigilance activities.

Aim/Objective: To classify the pre-authorized pharmacovigilance agreements according to the SFDA definition of advanced therapy medicinal products (ATMPs) and to evaluate the MAHs' response to the inspection team recommendation.

Methods: A retrospective observational study documenting various pre-authorized pharmacovigilance agreements was reviewed between March 2023 and March 2024. All submitted pharmacovigilance agreements were included to be classified into Advanced Therapy Medicinal Products related agreements where the Advanced Therapy defined as any of medicinal products for human use: Gene therapy, Cell-based medicinal product, and Combined ATMP products contain as an integral part of the product. The agreements were evaluated based on the approval status, the number of attempts, and the duration to approve the agreement.

Results: A total of 75 pre-authorized pharmacovigilance agreements were examined; among them, 20% (15 agreements) were associated with Advanced Therapeutics-related Marketing Authorization Holders (MAHs). Of these 15 agreements, 53% (8) were successfully approved, with approval durations ranging from 1 to 137 days. The number of attempts this includes any revisions made in response to SFDA inquiries to secure approval for these agreements ranged from 0 to 4. The comments varied between there was no pharmacovigilance agreement submitted and no clarity on who will do the local pharmacovigilance activities to certain specifications like the accessibility to the global safety database and handling of local ICSR cases, the PSSF preparation and the accessibility to the global PSMF, signal screening, literature review, the external audit frequency.

Conclusion: These findings emphasize the importance of addressing these concerns to strengthen pharmacovigilance practices. Clear guidelines and regulations are needed to ensure the submission and proper execution of pharmacovigilance agreements, the effective management of safety data, and compliance with international standards.

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A Risk Minimization Tool for Drug Exposure During Pregnancy: A Multidisciplinary Approach to Reassess The Pregnancy Pictogram on Medication Packaging

Mehdi Benkebil[1], Alain Balley[2], Sylvain Bouquet[3], Jérôme Massardier[4], Emilie Vittaz[1], Dominique Masset[1], Leslie Alcaraz[1], Fatiha Karam[1], Céline Mounier[1], Thierry Vial[1], Agnès Laforest-Bruneaux[1]

[1]ANSM, Saint Denis, France. [2]Famille Rurales, Fédération Nationale, Paris, France. [3]Collège de la Médecine Générale, Paris, France. [4]Hospices Civils de Lyon, Femme Mere Enfant University Hospital France; Department of Obstetrics and Gynecology, Lyon, France

Introduction: In 2017, France introduced a system of "Pregnant Women" pictograms affixed on outer packaging of medicinal product to reinforce information for patients and healthcare professionals. Two types of pictograms ("Prohibited" or "Danger"), differentiated according to the existence or absence of a safer therapeutic alternative in the event of pregnancy, can be affixed. With the aim of improving the current system, French National Agency for the Safety of Medicines and Health Products (ANSM) was commissioned by the health ministry to re-evaluate the existing system.

Aim/Objective: To reassess the relevance of a pictogram and the type of type of recommendation to be affixed on the packaging of a medicinal product in relation to its harmful effects on the unborn child.

Methods: ANSM set up a multidisciplinary Temporary Scientific Committee (TSC) in 2023 to help make informed decisions and develop proposals to improve the current system. The method was to adapt the system based on an assessment of the current situation. A number of tools were used to carry out this review such as consultation of stakeholders through public hearings, a call for written contributions and an opinion survey among a representative sample of women from the general population and selected stakeholders for interviews.

Results: Thirteen technical meetings of the TSC were organized over a 13-month period. Sixty-eight entities were selected to submit written contributions. Three countries were invited to share their experiences on a similar risk minimization tool.

The TSC retained four types of risk for the unborn child associated with medicines used during pregnancy: teratogenicity, foetotoxicity, miscarriage and neurodevelopmental disorders. For each of these outcomes, four levels of risk were retained according to the available animal data and human studies: proven risk, suspected risk, undetermined risk, unsuggested risk. Information currently contained in the Summary of Product Characteristics of the drug was the basis for this classification.

The TSC proposed that the pictogram should take the form of a visual image of a pregnant woman with a colored visual scale representing the current knowledge of the risk level of the medicinal product. The pictogram will be accompanied by a text informing on the risk level and suggesting recommendations according to the level of representation of the pictogram

Conclusion: ANSM, as a scientific and regulatory agency, has innovated in its approach by trying to have a 360° vision on a public health and societal issue. This has required the use of a wide range of competencies, particularly scientific, patient perception and literacy skills. A key success factors for the implementation and reevaluation of health public policy actions is a multidisciplinary approach within a scientific committee, contribution of various stakeholder and the use of multiple tools. The aim is to provide a comprehensive system for patients and HCPs.

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Integration of Electronic TB Register (EDRWeB) and Pharmacovigilance Monitoring System (PViMS) to Improve Clinica Governance

Mulatedzi Makhado[1], Mukesh Dheda[2]

[1]Aurum Institute, Johannesburg, South Africa. [2]National Department of Health, Pretoria, South Africa

Introduction: South Africa has implemented an Electronic Drug Resistant software (EDRWeb), a web-based software used for the surveillance and management of Drug Resistance Tuberculosis. The software contained a component for documenting adverse drug reactions (ADR), but it was not entirely compatible with the Pharmacovigilance Monitoring System (PViMS), necessitating development and system modifications to simplify data sharing for causality assessment and improve clinical governance.

Aim/Objective: The aim of the study is to strengthen the recording of ADR's on EDRWeB and the use of PViMS to support active Drug Safety Monitoring (aDSM) program in South Africa.
Methods: The method entailed examining the adverse drug reactions module of EDRWEB and identifying areas that needed to be improved in order to be integrated with PViMS. The National Pharmacovigilance Centre, implementing partners, and the systems development team met multiple times to come to an agreement on improvements that would be made to the system's functionality. The system development team received a summary and structure of the enhancements for adverse drug reactions module. Monitoring and evaluation of the completed tasks were performed to ensure that enhancements were conducted according to specifications.
Results: All ADR fields with free text format such as suspected medicines, interventions made or ADR grading, have been replaced by drop downs options. In the upgraded version of EDRWEB, which automatically populates demographic data for patients, a standard adverse drug reaction form developed by South Africa's Health Products Regulatory Authority (SAHPRA) has been integrated thereby reducing the time needed to complete this form to about two minutes. All essential medicines on the Health Products Master List have been added to the database, making it easier for data capturer or healthcare professional to search and select a suspected medicine in addition to tuberculosis medicines that existed on EDRWEB. Though no demographics are captured when a new event is registered, the system can generate a completed ADR form in a standard format making it easy to share with SAHPRA through email for further processes.
Conclusion: An efficient system with the participation of all relevant stakeholders is needed to improve detection, recording and reporting of adverse drug reactions, to improve clinical governance.
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Comprehensive Analysis of Pharmacovigilance Inspections Findings: Focus oninspection Topics in the Pharmaceutical Industry in Saudi Arabia

Abdullatif AlOtaibi, Amal Arafah, Hammad Al Dali

Saudi FDA, Riyadh, Saudi Arabia

Introduction: Pharmacovigilance is a critical component of pharmaceutical safety, it involves monitoring and assessing the safety of pharmaceutical products post-approval. The Saudi Food and Drug Authority (SFDA) regulates and ensures compliance with pharmacovigilance practices among Marketing Authorization Holders (MAHs) in Saudi Arabia.
Aim/Objective: This study aimed to comprehensively analyze inspection findings among International MAHs, Regional MAHs, and Local MAHs and highlight areas of concern within the inspection topics of MAHs in Saudi Arabia.
Methods: A descriptive secondary data analysis was performed to examine inspection reports from the SFDA between January 2019 and December 2022. All MAHs submitted to regulatory inspections by the SFDA were included. The MAHs were categorized into three groups according to their countries of origin: International MAHs, Regional MAHs, and Local MAHs.
Results: The study analyzed 1122 inspection findings from 2019 to 2022, categorized based on severity and MAH type. International MAHs had the highest number [498, (46.7%)], with Major findings being the highest proportion in all [704, (62.7%)] MAH types. Additionally, management and signal management consistently emerged as a top inspection topic.
Conclusion: The analysis of MAHs and their inspection findings between 2019 and 2022 has revealed that international MAHs consistently reported higher inspection findings than regional and local MAHs. More inspection findings in regional MAHs than in local MAHs highlight the impact of regional guidelines, regulatory interpretations, resource constraints, and communication challenges on inspection outcomes. The lack of harmonization in pharmacovigilance systems between Saudi Arabia and neighboring countries further might contributed to major findings, emphasizing the need for alignment with global pharmacovigilance standards. Moreover, areas for improvement were identified, such as management and reporting adverse reactions.
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Comparative Safety Analysis of Serious Adverse Drug Events in North America: A 19-Year Study of FDA and Canadian Vigilance Databases

Niaz Chalabianloo[1,2,3], Kamran Sedig[3], Flory Tsobo Muanda[1,2,4,5]

[1]Department of Physiology and Pharmacology, Western University, London, Canada. [2]ICES Western, London, Canada. [3]Department of Computer Science, Western University, London, Canada. [4]Lawson Health Research Institute, London, Canada. [5]Department of Epidemiology & Biostatistics, Western University, London, Canada

Introduction: Adverse drug events (ADEs) pose significant public health concerns and are closely monitored by regulatory agencies. [1] Comparing ADEs databases across countries can provide valuable insights into reporting patterns, medication usage, and patient safety.

Aim/Objective: To compare the prevalence and patterns of serious ADEs reported in the United States (OpenFDA) and Canada (Canada Vigilance) by year, age groups, and gender and identify the top medications and reactions associated with ADRs.
Methods: Data on reported medications, ADEs, and outcomes were obtained from the OpenFDA and Canada Vigilance databases from 2004Q3 to 2023Q3. We used generic and brand names for medications and the Medical Dictionary for Regulatory Activities (MedDRA)-v24 preferred terms for adverse drug events (ADEs). The adjusted prevalence of serious ADEs per year (standardized prevalence per 100,000 people) during the study period and the prevalence of ADEs by age and gender were calculated and compared between the two countries.
Top medications associated with serious ADERs overall and by specific outcomes (e.g., death, hospitalization, disability) were identified. The most common types of serious adverse events overall and by specific outcomes were also determined. Descriptive statistics (Chi-square tests, p-values) and trend analysis (Cochran-Armitage and Linear Regression trend analysis) were used to compare data from the United States and Canada; chi-square tests.
Results: The prevalence of adjusted adverse drug events (ADEs) significantly increased over the study period in both Canadian and United States databases. A higher proportion of serious ADEs was observed among females (United States: 55% [5,692,923/10,308,253]; Canada: 60% [730,540/1,220,677]) and individuals aged 45 and above (United States: 74% [3,049,262/4,113,110]; Canada: 68% [708,954/1,045,305]), consistently across both databases. Adalimumab, aspirin, and prednisone were among the top 10 medications shared between Canada and the United States. Notably, oxycodone (4.0%) accounted for the highest prevalence of reported medication-related deaths in the United States, while clozapine (5.5%) held this distinction in Canadian databases during the study period. Pneumonia emerged as the most frequent serious ADE leading to hospitalization, with rates of 4.0% in Canada and 2.3% in the United States databases.
Conclusion: The present comparative study showed similarities and disparities in the prevalence and patterns of ADE in the United States and Canada. This highlights the importance of cross-country comparisons in uncovering potential drug safety concerns and identifying high-risk populations.
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Use of methylphenidate and reporting of valvular heart disease: global pharmacovigilance analysis in children and adults

Estelle Ayme-Dietrich[1], Florentia Kaguelidou[2], Gilles Bertschy[1], Laurent Chouchana[3]

[1]Université de Strasbourg, Strasbourg, France. [2]Université Paris Cité, Paris, France. [3]Assistance Publique - Hopitaux de Paris, Paris, France

Introduction: Methylphenidate (MPH) is a common treatment of attention-deficit/hyperactivity disorder (ADHD). Concerns have been raised regarding its cardiovascular safety, partly in relation with its micromolar affinity for the 5-HT2B receptor, whose activation may result in valvular heart disease (VHD).
Aim/Objective: To explore the association between the use of MPH and VHD reporting in children and adults.
Methods: We performed a disproportionality analysis within the WHO global safety database (VigiBase) using data, since inception until March 6th 2024, from: i) full database and ii) different age groups (children/adolescents 6-17 years; adults 18-64 years). To avoid competition bias, safety reports with amphetamine-like appetite suppressants were excluded. Disproportionality was expressed using reporting odds-ratio (ROR) and its 95% confidence interval (CI).
Results: Of 29,129 spontaneous reports with MPH, 23 (7.9 per 10,000 reports) VHD cases were identified, including 13 adults and 10 children. Most cases concerned injury on mitral valve. A disproportionate reporting was observed overall (ROR 1.6, 95% CI 1.1-2.4). Analysis according to age group found that disproportionality in VHD reporting was not found in children and adolescents (ROR 1.7, 95% CI 0.9-3.2) but in adults only (ROR 2.7, 95% CI 1.6-4.7). Furthermore, amongst MPH users only, VHD reporting was higher in adults compared to children (ROR 2.7, 95% CI 1.2-6.3).
Conclusion: VHD reporting appears rare with MPH compared to other adverse events and is increased only in adults. Our findings support a potential safety signal of VHD in adults exposed to MPH. A risk in that population cannot be excluded, requiring further assessment.
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Safety of Ifosfamide During Pregnancy: A Comprehensive Analysis

Charlotte Devant[1], Tessa Pietri[2], Marine Auffret[3], Laurence Lagarce[4], Mathilde Barrois[1], Jean-Marc Treluyer[5], Vassilis Tsatsaris[5], Laurent Chouchana[1]

[1]Assistance Publique - Hopitaux de Paris, Paris, France. [2]Assistance Publique - Hopitaux de Marseille, Marseille, France. [3]Université Claude Bernard Lyon 1, Lyon, France. [4]CHU Angers, Angers, France. [5]Université Paris Cité, Paris, France

Introduction: Ifosfamide, an alkylating agent, is cornerstone in the treatment of high-grade sarcomas. In rare circumstance, these malignancies can affect women during pregnancy. Although aggressive treatment is critical, available data regarding the safety of ifosfamide for the fetus are limited.
Aim/Objective: The objective of this study is to assess the safety for the fetus and the future child of ifosfamide treatment during pregnancy.
Methods: First, we performed a case-by-case review of the cases related to ifosfamide use during pregnancy, spontaneously reported in the French Pharmacovigilance Database. Second, we reviewed cases from the literature. Finally, we performed a disproportionality analysis on VigiBase, the WHO global safety database, to assess the association between ifosfamide and selected adverse events. The results are expressed as reporting odds-ratio (ROR) with a 95% confidence interval (CI).
Results: A total of 27 cases of ifosfamide use during pregnancy were identified. Obstetrical complications were intrauterine growth retardation (IUGR) (n = 15, 56%) and oligohydramnios or anhydramnios (n = 15, 56%). Pregnancy outcome was intrauterine fetal demise (IUFD) in 5 (19%) cases, all being treated with ifosfamide before the 21th week of gestation. All livebirths (n = 22) were preterm, associated with neonatal acute renal failure (ARF) in 5 (23%) cases. In addition, 3 (14%) neonatal deaths were reported within the first week of life in neonates having anuria. In VigiBase, which has over 263,145 spontaneous reports on pregnancy topics, we found a significant increased reporting of oligohydramnios (ROR 8.3 [4.5-15.2]), IUGR (ROR 4.2 [2.7-6.6]) and neonatal renal failure (ROR 3.8 [1.2-12.4]) with ifosfamide compared to other antineoplastic agents.
Conclusion: Altogether, this comprehensive analysis supports that ifosfamide may induce fetal nephrotoxicity in pregnant women. It can result in oligohydramnios, IUGR, neonatal ARF and, in case of exposure during the first half of pregnancy, IUFD. Close monitoring by fetal ultrasounds may help to detect early fetal toxicity.

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Magnitude and Predictors of Drug Therapy Problems Among Patients with Leukemia at a National Referral Hospital in Kenya.

Brian Savwa[1,2], Peter Karimi[2], David Nyamu[2]

[1]Kenyatta National Hospital, Kenya, Kenya. [2]University of Nairobi, Nairobi, Kenya

Introduction: Drug therapy problems (DTP) are undesirable effects and experiences that occur to a patient during drug treatment and tend to alter the desired therapeutic outcomes (1-3).Patients with leukemia are susceptible to DTPs due to the use of multiple cytotoxic drugs and long periods of treatment. (3,6).Several studies conducted among cancer patients show high prevalence of DTPs among these patients (1-7).The number of factors that may predict occurrence may be patient related and treatment related factors (5). There is limited data on drug therapy problems among leukemia patients in sub-Saharan Africa.

Aim/Objective: 1. To describe the types and magnitude of drug therapy problems among patients with leukemia.

2. To analyze the effect of Sociodemographic factors on DTPs among patients with Leukemia.

3. To examine the influence of Clinical factors on DTPs among patients with leukemia.

Methods: A cross-sectional study was perfomed on a random sample of patients with leukemia at inpatient oncology units at a National referral hospital in Kenya. A calculated sample of 100 patients was targeted but only 89 participants were enrolled for the period between March 2023 to August 2023.Data for the dependent and independent variables was collected via a questionnaire through interviews and from medical records. Independent variables included the sociodemographics factors;age,gender,health insurance cover, education level, employment status and the clinical factors included type of leukemia, disease status,comorbidity,phase of treatment, chemotherapy regimen and length of hospital stay. The dependent variables were the seven drug therapy problems as classified by Cipolle and Strand criteria 2012 (8). Descriptive statistics and logistics regression was done using STATA software version 15.

Results: The result showed that among all the participants that were assessed (n = 89) ,91% had drug therapy problem (n = 81). A total of 204 DTPs were identified at an average of 2.5 per patient. Adverse drug reaction (88.8%),non-compliance (58.4%) and need for additional therapy (37.1%) were the major types of therapy problems identified. Unnecessary drug therapy (14.6%),dose too low (13.5%) ,Ineffective drug therapy (11.2%) and dose too high (5.6%) were the other types of DTPs identified. Among the various factors assessed, significant predictors of DTPs were age, employment status, phase of treatment and chemotherapy regimens. Age of participants was a significant predictor of occurrence of adverse drug reaction and non-compliance. Employment status was significantly associated with non-compliance. Phase of treatment influenced compliance to therapy while chemotherapy regimen influenced need for additional therapy and ineffective drug therapy problem.

Conclusion: The study established the presence of high prevalence of drug therapy problems among patients with leukemia. Patient demographics and clinical factors influenced occurrence of dug therapy problems. Thus, tailored drug therapy problem assesment tools should be incorporated as part of care for leukemia patients with predictor factors as baseline guide.

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Trimethoprim/sulfamethoxazole and Risk of Acute Respiratory Failure in Youth and Adolescents: A Disproportionality Analysis

Fatemeh Ahmadi[1,2], Niaz Chalabianloo[1], Eric McArthur[2], Flory T Muanda[1,2,3]

[1]Western University, London, Canada. [2]ICES Western, London, Canada. [3]. Lawson Health Research Institute, London Health Sciences Centre, London, Canada

Introduction: The US FDA (Food and Drug Administration) recently issued a warning on the labelling of trimethoprim/sulfamethoxazole (TMP-SMX) for pediatrics (1) . The warning was based on a case series published in 2019, which reported five adolescent cases of acute respiratory failure due to TMP-SMX (2). However, to date, no comparative study has been conducted to investigate this issue. Using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, we conducted an active-comparator restricted disproportionality analysis to quantify the risk of acute respiratory failure with TMP-SMX.

Aim/Objective: To investigate whether TMP-SMX use in youth and adolescents is associated with a higher risk of acute respiratory failure than other medications.

Methods: We analyzed adverse drug events (ADEs) reported to FAERS databases for individuals between 10 and 24 years old from 2004Q1 to 2023Q4 using SAS enterprise guide 8.3. The outcome of interest was a composite of the Medical Dictionary for Regulatory Activities (MedDRA)-v24 preferred terms 'acute respiratory failure' and 'acute respiratory distress syndrome.' We used reporting odds ratios (ROR) to compare the proportion of the composite outcome reports for TMP-SMX to the composite outcome for the following active comparator groups: azithromycin or amoxicillin/clavulanic acid. All analyses were restricted to ADEs considered the primary suspects in the database.

Results: There were 810 reports of ADEs with TMP-SMX in youth and adolescents. The median age was 18 (15 to 21) years, and 453 (56%) of the individuals were female. Among 42 reports of the composite outcome of 'acute respiratory failure' and 'acute respiratory distress syndrome', the most reported indication (71%) was acne. Our study showed that TMP-SMX (42 cases of 810 [5.19%] vs. 11 cases of 1,617 [0.68%]; ROR, 7.98 [95% CI, 4.09 to 15.59]) had a

higher proportion of composite of 'acute respiratory failure' and 'acute respiratory distress syndrome' reports compared to azithromycin. No reports of the composite outcome were found with amoxicillin/clavulanic acid, which precluded further analyses.
Conclusion: TMP-SMX may be associated with a higher risk of acute respiratory failure in youth and adolescents. These findings require further pharmacoepidemiologic studies to be confirmed.
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The Implementation of KPI (Key Performance Indicators) to Manage the Pharmacovigilance System of a Public Vaccine Producer in Brazil

Mayra Oliveira[1,2], Fernanda Oliveira[1], Vera Gattás[1], Clarissa Santos[1], Maria Beatriz Lucchesi[1], Monica Taminato[2]

[1]Instituto Butantan, São Paulo, Brazil. [2]Federal University of Sao Paulo, São Paulo, Brazil

Introduction: Background: Pharmacovigilance is a science that acts in favor of patient safety, its system must be robust, efficient, and frequently evaluated to ensure its continuous improvement. Key performance indicators (KPI) are a set of quantifiable measures that assess the performance of companies, processes, and systems, such as Pharmacovigilance. [1-5]
Aim/Objective: Aim: To implement and evaluate the results of KPI to the Pharmacovigilance system of a public vaccine producer in Brazil to identify opportunities for improving this system, to keep it efficient, and to continuously enhance it.
Methods: Methods: A systematic review and benchmarking with pharmaceutical company representatives were carried out to guide the selection process of KPIs and their rationale to be implemented in the PV System of Instituto Butantan. The KPIs defined by the methods described previously were validated by a consensus formed by 6 experts. To implement the indicators, a dashboard was created and the KPIs, their goals, measurements, and evaluation periodicity were described in the institution's Standard Operating Procedure (SOP).[6]
Results: Results: From the systematic review, only one of the KPIs identified was appropriate for measuring the processes of the PV System of a Marketing Authorization Holder (MAH). After the interviews with pharmaceutical company representatives which are operating in Brazil, 25 KPIs were identified. And just one matched with the one identified in the systematic review. These 25 KPIs were presented to 6 experts in a consensus meeting and all were approved after adjustments. As a pilot, 10 KPIs were implemented: number of individual case safety reports (ICSR) (1); ICSR per product (2); serious adverse event (SAE) reported per product (3); source of the report (4); number of Butantan's employees trained in PV course; number of on-time report for Regulatory Authority of ICSR (6), death or life-threatening reports (7) and Suspected Unexpected Serious Adverse Reaction (SUSAR) (8); ICRS reported to contracted partners on time (9) and number of corrective action and preventive action (CAPA) closed on time (10). A dashboard was developed to monitor and monthly evaluate the 10 KPIs during 2022 and 2023.
Conclusion: Conclusion: Two years after the implementation and evaluation of the KPIs, the importance of measuring the PV processes and the impacts on the PV system was demonstrated. Through the regular evaluation, some improvements could be placed in the routine and even the tools used in the PV system were improved. Based on the pilot results, the viability of implementing other KPIs selected is under evaluation.
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Pre-Existing Comorbidities as Risk Factors for Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination in Young Males: An Observed Versus Expected Analysis

Mohammed Salem[1], Yola Moride[2,3], Bernard Bégaud[4]

[1]Rutgers New Jersey Medical School, Newark, USA. [2]Université de Montréal, Montreal, Quebec, Canada. [3]Rutgers School of Public Health, New Brunswick, USA. [4]University of Bordeaux, Nouvelle-Aquitaine, France

Introduction: Studies have linked mRNA vaccines to rare cases of myocarditis and pericarditis, with a higher number of cases in males under 30 years old [1]. The underlying mechanisms remain unclear, but one potential explanation is a higher prevalence of comorbidities with cardiovascular burden, such as hypertension, diabetes, dyslipidemia, and obesity in these cases compared to similarly aged vaccinees who did not develop these adverse events.
Aim/Objective: To determine whether the prevalence of common chronic comorbidities with cardiovascular burden (hypertension, diabetes, dyslipidemia, and obesity) is significantly higher in 18–30-year-old males with reports of myocarditis or pericarditis suspected to be caused by mRNA COVID-19 vaccines compared to the vaccinated population or the general population.
Methods: Using an observed versus expected analysis, we compared comorbidity rates among 18-30-year-old males with post-vaccination myocarditis or pericarditis in VAERS (2021-2022) against rates in vaccinated individuals from concurrent epidemiological studies and pre-2021 general population data. Due to the limitations in national estimates and available literature and lack of accessible statistics specific for males in the 18–30-year age group, we compared the observed rates in VAERS cases against a spectrum of estimates that included various age groups and datasets, covering vaccinated and general populations, and both genders.
Results: Among the 359 myocarditis and pericarditis cases identified in VAERS, prevalence rates for hypertension, diabetes, dyslipidemia, and obesity were found to be notably low, at 0.6%, 0.8%, 1.4%, and 2.5%, respectively. Our investigation revealed that the prevalence of hypertension, diabetes, dyslipidemia, and obesity in VAERS cases fell below even the lowest estimates reported across these diverse data sources (15.2-37.9%, 4.4-25.5%, 19.1-29.5%, and 4.0-39.9%, respectively) [2–6].

Conclusion: Despite the important under-documentation of comorbidities in VAERS, the low prevalence of cardiovascular risk factors observed in this study does not suggest a possible confounding by comorbidities in the association between COVID-19 vaccination and myocarditis/pericarditis. The lower comorbidity prevalence in the 18-30 age group, typically healthier than older adults, might skew comparisons with literature data that includes data with older adults. Furthermore, comparing findings from VAERS against literature data that combines data from both males and females complicates interpretation. Nevertheless, the notable disparities between VAERS data and existing literature underscore the need for more comprehensive and nuanced data on the characteristics of mRNA vaccine recipients, particularly when stratified by age and sex, to inform future research and public health interventions.

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Safety Signal Detection of Hepatocellular Injury Following Methotrexate Administration in Children with Cancer and Rare Diseases

Masayoshi Nakakuni[1,2], Kosuke Nakano[1], Seiji Mitsui[1], Naoko Deguchi[1], Seiko Miyazaki[1,2]

[1]Center for Clinical Research and Development, National Center for Child Health and Development, Tokyo, Japan. [2]Social Pharmacy and Regulatory Science, Syowa Pharmaceutical University, Tokyo, Japan

Introduction: Methotrexate is used in the treatment of various pediatric diseases, including juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), and cancer. However, although elevated alanine aminotransferase (ALT) levels are a well-known side effect of methotrexate, its incidence for each condition is different. [1-3]

Aim/Objective: To detect safety signals associated with abnormally elevated ALT levels in children treated with methotrexate for JIA, IBD, or cancer.

Methods: We conducted an SCCS analysis involving patients aged 0–14 years who received methotrexate treatment following diagnosis of JIA, IBD, or cancer and subsequently developed plasma ALT ≥ 5 times the upper limit of normal from April 2016 to June 2021. Patient data were obtained from the pediatric medical information collection system (P-MICS), a Japanese electronic medical records database. A conditional Poisson regression model was used to estimate the age-adjusted incident rate ratio (IRR) between risk periods versus baseline periods within individuals. This analysis was performed to evaluate signals occurring within seven days of methotrexate administration. The IRR and cumulative occurrences of elevated ALT levels after methotrexate administration per calendar month were calculated using SCCS with SAS software version 14.0.

Results: Among 1,175 methotrexate users with the indication. Compared to the baseline period, an increased risk of elevated ALT levels was observed following methotrexate administration in 558 patients with cancer (IRR 2.41; 95% confidence interval [CI] 2.15–2.70), but no increased risk was observed in 27 patients with JIA (IRR 0.79; 95% CI 0.44–1.40) or 9 patients with IBD (IRR 2.82; 95% CI 0.62–12.80). The 95% lower band of the IRR was > 1 in 21 patients with cancer five months after the start of the study period.

Conclusion: An increased risk of elevated ALT levels was associated with methotrexate use in children with cancer. SCCS analysis is useful for detecting safety signals in a small number of pediatric patients with limited safety data.

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A Codesign Approach for Designing Qualitative Study for Exploring Knowledge and Attitudes Related to the Use of Antibiotics in Animals

Fátima Roque[1,2], Paula Oliveira[3,4], Ana Claudia Coelho[5,6], Adolfo Figueiras[7,8,9,10], Maria Teresa Herdeiro[11]

[1]BRIDGES - Biotechnology Research, Innovation and Design for Health Products,, Guarda, Portugal. [2]Research Laboratory on Epidemiology and Population Health, Polytechnic of Guarda, Guarda, Portugal. [3]Institute for Innovation, Capacity Building and Sustainability of Agri-food Production (Inov4Agro), University of Trás-os Montes and Alto Douro (UTAD),, Vila Real, Portugal. [4]Institute for Innovation, Capacity Building and Sustainability of Agri-food Production (Inov4Agro), University of Trás-os Montes and Alto Douro (UTAD), Guarda, Portugal. [5]Animal and Veterinary Research Centre, Department of Veterinary Sciences, University of Trás-os-Montes e Alto Douro (UTAD), Vila Real, Portugal. [6]Associate Laboratory for Animal and Veterinary Sciences (AL4AnimalS), Faculty of Veterinary Medicine, University of Lisbon, Lisboa, Portugal. [7]Department of Preventive Medicine and Public Health, University of Santiago de Compostela, 15702, Santiago de Compostela, Santiago de Compostela, Puerto Rico. [8]Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostaela, Sudan. [9]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiology and Public Health-CIBERESP), Madrid, Spain. [10]Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain. [11]Department of

Medical Sciences, Institute of Biomedicine (iBiMED), University of Aveiro, Aveiro, Portugal

Introduction: The inappropriate use of antibiotics in both humans and animals, as well as their environmental dissemination, is considered to be one of the main factors in bacterial resistance. Previous studies have proven that attitudes and knowledge underlying with prescribing and dispensing of antibiotics respectively by physicians and pharmacists [1, 2]. However, there is a lack of studies to understand what factors influence antibiotic prescription by veterinarians. Antibiotic resistance is a cross-transmission phenomenon between humans, animals, and the surrounding environment, combating it effectively requires a combined multidisciplinary approach and understanding the perceptions and attitudes of all stakeholders related to this important issue
Aim/Objective: Identify the topics to be addressed in a qualitative study in the form of focus groups with veterinarians to identify potential knowledge and attitudes related to antibiotic prescribing and bacterial resistance
Methods: A literature review about factors influencing the prescription of antibiotics in animal and human health following a co-design approach enrolling pharmacists veterinarians and researchers with experience in qualitative studies.
Results: A guide was drawn up to serve as a basis for the focus group discussion, which includes the following topics: (i) perceptions and importance given to bacterial resistance; (ii) antibiotics prescription practices; (iii) concerns about cross-transmission between humans, animals and environmental (iii) use of guidelines; (iv) needs of regulatory measures; (v) attribution of responsibilities; and (vi) implementation of ecopharmacovigilance stewards codesign proved to be a very effective methodology for designing the topics included in the guide and for the organization of focus groups sessions.
Conclusion: The codesign proved to be a very effective methodology for designing the topics included in the guide and for the organization of focus group sessions.
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Enhancing Public Awareness of Antibiotic Resistance Through Regulatory Agencies' Social Media Users Engagement in Portugal

Fátima Roque[1,2], Maria Teresa Herdeiro[3], Paulo Cachim[4], Vitor Roque[5]

[1]Biotechnology Research, Innovation and Design for Health Products (BRIDGES), Polytechnic of Guarda, Guarda, Portugal. [2]Research Laboratory on Epidemiology and Population Health, Polytechnic of Guarda, Guarda, Portugal. [3]Department of Medical Sciences, Institute of Biomedicine (iBiMED), University of Aveiro, Aveiro, Portugal. [4]University of Aveiro, Aveiro, Portugal. [5]Polytechnic of Guarda, Guarda, Portugal

Introduction: Antibiotic resistance is a major public health problem in domain of human, animal and environmental health. Inappropriate antibiotic use drives bacterial resistance escalation. Raising public awareness of this important public health issue is critical and social media can play a key role in this effort [1]. Regulatory agencies also bear the critical responsibility of educating and cautioning the population about the safe use of medications. In Portugal, the oversight of human-use medicines falls under the purview of the National Authority of Medicines and Health Products (INFARMED), while veterinary medicines are regulated by the General Directorate of Food and Veterinary (DGAV).
Aim/Objective: To analyze the content of the publications on the social network Facebook of INFARMED and DGAV on the inappropriate use of antibiotics and bacterial resistance.
Methods: A retrospective study of posts published about antibiotics between January 2021 and December 2023 on Facebook social network of INFARMED and DGAV. The search terms were "antibiotics", "bacterial resistance", and "antimicrobials". It was analyzed the type of publications and public engagement, and, additionally, a content analysis of publications was performed.
Results: During the study period, INFARMED published 69 posts and DGAV published 52 posts. The type of publication was mostly images (INFARMED - 54%; DGAV - 58%). The audience engagement included mainly likes (ranging from 0 to 76, for INFARMED posts and from 0 to 69 for DGAV posts) and shares (ranging from 0 to 29, for INFARMED posts and from 0 to 44 for DGAV posts). INFARMED published mainly posts concerning "Guidelines and Recommendations" for the appropriate use of antibiotics (N = 64; 93%) followed by "Innovation and Research on Antibiotics" and "Antibiotic Resistance" (N = 3; 3%) and DGAV published mainly posts concerning "Guidelines and Recommendations" for the appropriate use of antibiotics in veterinary (N = 32; 64%) followed by "Innovation and Research on Veterinary Antibiotics" (N = 18; 36%).
Conclusion: The number of posts related to antibiotic use and bacterial resistance was relatively low in both regulatory agencies, and, more importantly, the impact of publications measured by the public interaction, was very limited. No publications regarding ecopharmacovigilance were posted during the study period. For bigger public awareness regulatory agencies should promote the use of social networks to disseminate educational material on such important topics as antibiotic resistance, and increase their impact.
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Guideline for Antimicrobial Prescription in Food-producing Animals in OECD-related countries: a contribution for OneHealth

Ana Isabel Placido[1,2], Rafaela Nogueira[3,4], Alexandra Monteiro[1,2], Paula Oliveira[3,4], Ana Claudia Coelho[5,6], Adolfo Figueiras[7,8,9], Maria Teresa Herdeiro[10]

[1]BRIDGES - Biotechnology Research, Innovation and Design for Health Products, Guarda, Portugal. [2]Research Laboratory on Epidemiology and Population Health, Polytechnic of Guarda (IPG), Guarda, Portugal. [3]Centre for the Research and Technology of Agro-Environmental and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal. [4]Institute for Innovation, Capacity Building and Sustainability of Agri-food

Production (Inov4Agro), University of Trás-os Montes and Alto Douro (UTAD), Vila Real, Portugal. [5]Animal and Veterinary Research Centre, Department of Veterinary Sciences, University of Trás-os-Montes e Alto Douro (UTAD), Vila Real, Portugal. [6]Associate Laboratory for Animal and Veterinary Sciences (AL4AnimalS), Faculty of Veterinary Medicine, University of Lisbon, Lisboa, Portugal. [7]Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Sanmtiago de Compostela, Spain. [8]Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain. [9]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiology and Public Health-CIBERESP), Madrid, Spain. [10]8Department of Medical Sciences, Institute of Biomedicine (iBiMED), Guarda, Portugal

Introduction: Antimicrobials have been pivotal in safeguarding human, animal, and environmental health. Nevertheless, their inappropriate use in human and animal health, namely in food-producing animals has escalated to antimicrobial resistance (AMR), a global health problem [1]. In the scope of pharmacovigilance is important to understand how guidelines in the food-producing sector include AMR concerns for One-Health perspective.
Aim/Objective: To evaluate the implementation of guidelines for the prudent use of antimicrobials in food-producing animals of Organisation for Economic Co-operation and Development (OECD) members, candidates, and key partners.
Methods: We screened a total of 48 OECD-related countries for national guidelines on antimicrobial use in food-producing animals, including 38 members, five candidates, four key partners, and one country serving as both a candidate and a key partner.
Results: Among the 38 member countries, 26 (n = 26/38, 68%) had guidelines, totaling 51 collected guidelines. Most of them addressed antibiotic use (ABU) (n = 28/51, 55%), while 23 (n = 23/51, 45%) focused on antimicrobial use (AMU). Species-specific guidelines were encountered in 23-member countries (n = 23/26, 60%), covering bovine (n = 24/26, 63%), ovine (n = 17/26, 45%), equine (n = 15/26, 39%), and/or swine (n = 20/26, 53%). Within the five OECD candidates, three guidelines were collected from two countries, both focusing on AMU in non-specified species. Key partner countries all had guidelines, accounting a total of five guidelines, two (n = 2/5, 40%) focusing on ABU and three (n = 3/5, 60%) on AMU, and all addressed non-specified species, although one partner also provided guidance specifically tailored to swine production.
Conclusion: Despite OECD-related countries issuing guidelines, variability persists across species and in the main focus (AMU/ABU), particularly among candidates and key partners. Establishing standardized guidelines across all OECD-related nations is crucial to combat AMR and advance towards One Health.
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Rivaroxaban Risk Management: Qualitative Analysis of Portuguese Educational Materials

Ana Margarida Advinha[1,2,3], Margarida Perdigão[1,2], Filipe Alfaiate[1,4,5], João Paulo Fernandes[6], Márcia Silva[6], Manuel José Lopes[1,2,4]

[1]Pharmacovigilance Regional Unit of Center and North Alentejo, Évora, Portugal. [2]CHRC–Comprehensive Health Research Centre, Évora, Portugal. [3]School of Health and Human Development, University of Évora, Évora, Portugal. [4]Nursing School of S. João de Deus, University of Évora, Évora, Portugal. [5]Hospital Espírito Santo of Évora - Alentejo Central Local Health Unit, Évora, Portugal. [6]INFARMED - National Authority of Medicines and Health Products, I.P., Lisboa, Portugal

Introduction: Given the significance of implementing additional risk minimization measures and the critical role of educational materials concerning rivaroxaban, effective dissemination and understanding of safety information are imperative to protect both individual and public health (1, 2).
Aim/Objective: To analyze the rivaroxaban prescriber's guide (PG) and patient alert card (PAC), evaluating their legibility, intelligibility, and comprehension, as well as how this information is transmitted and understood by healthcare professionals and patients, in Portugal.
Methods: In the first phase, the readability and intelligibility of the text of the educational materials under study were assessed using text analysis. The second phase consisted of assessing the readability, knowledge, access, comprehension, application, and access of the written and illustrated information in the documents, by carrying out individual semi-structured interviews with the main target audiences (prescribers and patients) and focus groups with pharmacists and nurses, as professionals who are also involved in patient care and education process. Software's used were ALT, Coh-Metrix-Port 2.0, and MAXQDA-24.
Results: Both the PG and the PAC showed a medium level of readability and intelligibility. In terms of lexical analysis, it was found that the texts of the educational materials place special emphasis on issues related to taking the medication, as well as those related to risk management, particularly bleeding. More than half of the doctors interviewed reported not using the PG. It stands out that doctors were more aware of the existence of the PG while most pharmacists and nurses were more aware of the PAC. All professionals were unanimous about the importance of the existence of educational materials for rivaroxaban. Most of the pharmacists and nurses reported not having access to educational materials in their practice and believe that their use is an asset in their practice. Only 50% of the patients interviewed were aware of the card and, of these, the majority said they had never used the PAC. However, those who habitually carry this material with them say that they feel it has had a positive impact on their use of the medicine.
Conclusion: Generally, healthcare professionals and patients considered the educational materials to be materials that are legible, and intelligible, with an appropriate design and typographic factors. What stands out is the doctors' lack of knowledge and reading of the educational material aimed at them - the PG. As for the patients' readability, only three had read the educational material aimed at them - PAC. This study was the starting point from which a pilot intervention will be developed to test new educational formats with patients and healthcare professionals.
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Evaluating Machine Learning Models for Predicting Saudi Pharmacovigilance Risk Management Measures

Mohammed Fouda, Leen Aldhalaan, Naser Al Jaser

Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Introduction: Pharmacovigilance plays a pivotal role in ensuring drug safety and efficacy post-market. The prediction of risk management measures (RMMs) is essential for timely intervention and patient safety. Recent advancements in machine learning (ML) offer promising tools to enhance these predictions, yet their comparative effectiveness in the domain of pharmacovigilance remains underexplored.
Aim/Objective: This study aims to compare the effectiveness of two ML models, XGBoost and Support Vector Machine (SVM), in predicting RMMs released by Saudi Food and Drug Authority (SFDA) based on drug characteristics, to identify the most suitable model for enhancing pharmacovigilance efforts.
Methods: We utilized a dataset encompassing various drug attributes and associated risks, employing a multi-label classification approach. Each model's performance was assessed through the F1 score (Micro) and Hamming Loss metrics, following hyperparameter tuning via GridSearchCV to optimize model performance.
Results: Our analysis demonstrated that the SVM model surpassed the XGBoost model in predicting RMMs, evidenced by a higher F1 score of 0.707 and a lower Hamming Loss of 0.069. These results highlight the SVM model's superior accuracy and reduced frequency of incorrect label predictions in the context of multi-label pharmacovigilance data.
Conclusion: The study underscores the potential of applying ML models, particularly SVM, to predict RMMs accurately, thereby supporting regulatory efforts and improving patient safety. Future research should explore integrating diverse datasets and advanced model tuning strategies to further refine prediction accuracy. The findings contribute to the burgeoning field of ML applications in pharmacovigilance, offering valuable insights for healthcare professionals and regulatory bodies.
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Spontaneous Reporting of Adverse Reactions Related to Antiplatelet Drugs in Saudi Arabia

AlHanouf AlDajani, Muhanad Alharbi, Fotoun Alblowi

food and drug Authority, riyadh, Saudi Arabia

Introduction: the Saudi Food and Drug Authority (SFDA) is the regulatory authority responsible for overseeing the safety, efficacy, and quality of drugs and medical devices in Saudi Arabia.
Antiplatelet drugs such as aspirin, clopidogrel, and ticagrelor, are key therapeutic agents in the treatment of cardiovascular diseases, these drugs under of the SFDA and are regulated in Saudi Arabia.

The SFDA actively encourages healthcare professionals, patients, and consumers to report any adverse events or side effects associated with the use of antiplatelet drugs or any other medications, these reports are collected and analyzed by the Saudi vigilance system.
Aim/Objective: to analyze spontaneous reports of adverse drug reactions (ADRs) related to antiplatelet drugs in Saudi Arabia, as well as to assess the seriousness and outcomes associated with these drugs, we will utilize the spontaneous reporting system of the Saudi Food and Drug Authority (SFDA).
Methods: A retrospective cross-sectional study was conducted to examine the rate of adverse drug reactions (ADRs), their seriousness, and outcomes associated with all antiplatelet drugs. The study analyzed spontaneous reports submitted by healthcare professionals through the SFDA electronic reporting system between January 1 and December 31, 2023. All received reports were exported into a Microsoft Excel spreadsheet. Reports related to antiplatelet drugs and ADRs were excluded from the analysis.
Results: Among the 267,818 spontaneous reports submitted by healthcare professionals, 5,843 were related to the use of antiplatelet drugs during the study period. The majority of adverse drug reactions (ADRs) occurred in males (60%), followed by females (38%), and the remaining cases had an unknown gender (2%). Acetylsalicylic acid had the highest number of reports with 4,265, followed by aspirin with 866 reports, clopidogrel with 801 reports, and ticagrelor with 70 reports. Out of all the reported ADRs, 19 were classified as serious. The most common ADR associated with antiplatelet drugs was heartburn, with 1,004 reports. This was followed by stomach ache with 704 reports and hemoglobin decrease with 448 reports. It is worth noting that the highest percentage of patients reported recovering from these ADRs.
Conclusion: The number of adverse drug reaction reports related to oral antiplatelets was low. Most of the adverse drug reactions associated with antiplatelets are non-serious.
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Saudi food and drug authority (SFDA) reporting system.

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Antipsychotic Abuse and Dependence: A 10-year Review of Reports to the European Pharmacovigilance System

João Paulo Fernandes[1,2,3], Pedro Benjamim[4], Márcia Silva[1], Bruno Sepodes[2,3], Carla Torre[2,3]

[1]INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon, Portugal. [2]Faculdade de Farmácia, Universidade de Lisboa, Lisbon, Portugal. [3]Laboratory of Systems Integration Pharmacology, Clinical and Regulatory Science, Research Institute for Medicines of the University of Lisbon (iMED.ULisboa), Lisbon, Portugal. [4]MD Clinical Pharmacology Unit, Santa Maria Local Health Unit, Lisbon, Portugal

Introduction: The phenomenon of antipsychotic abuse and dependence holds substantial implications for public health, intersecting with concerns regarding mental health management and societal responses to substance misuse [1, 2]. Understanding and addressing this issue is crucial for safeguarding the health and well-being of affected individuals.
Aim/Objective: To assess Individual Case Safety Reports (ICSRs) associated with antipsychotic abuse and dependence reported to the European Pharmacovigilance System over the last 10 years.
Methods: We conducted a retrospective analysis of ICSRs containing at least one medicinal product classified under the Anatomical Therapeutic Chemical (ATC) group NO5A (antipsychotics), reported as suspect or interacting to the EudraVigilance database, from January 1, 2014, to December 31, 2023. ICSRs with at least one MedDRA Preferred Term (PT) under the Standardised MedDRA Query (SMQ) narrow terms "Drug abuse and dependence" were included. The number of ICSRs per ATC 4th and 5th level was measured, along with patient demographic data, category of adverse drug reaction (MedDRA PT), seriousness, and the type of pharmacological substance reported concomitantly. Descriptive methods were used for statistical analysis.
Results: A total of 8613 ICSRs were identified, with 52.4% (n = 4512) of these concerning women and 71.0% (n = 6113) involving individuals aged between 18 and 64 years old. Among the ICSRs, the

majority (57.1%; n = 4914), contained at least one medicinal product classified under the ATC group N05AH (diazepines, oxazepines, thiazepines, and oxepines), with quetiapine being the most reported medicinal product, representing 36.7% (n = 3164) of the total reports. Regarding seriousness, 95.3% (n = 8205) of the ICSRs were classified as serious, with 39.7% (n = 3420) leading to hospitalization and 13.9% (n = 1201) resulting in the death of the individual. One-fifth of the reports (n = 1735) were related to cases of suicide attempt. Somnolence was the most frequently reported adverse drug reaction, occurring in 11.4% (n = 984) of cases. The most frequently reported therapeutic classes concomitantly were antidepressants, anxiolytics, and antiepileptics, noting that approximately 8% (n = 662) of the ICSRs referred to the concurrent use of ethanol, cocaine, or cannabis.
Conclusion: Our findings reinforce the urgent need to address antipsychotic abuse and dependence, given their profound societal implications. Furthermore, it is important to note that the extent of this issue may exceed our current understanding, due to potential underreporting and the influence of existing pharmacovigilance regulations.

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Pharmacovigilance of Innovative Long-Acting Injectable Antiretroviral Therapy: A Post-marketing Retrospective Study

Anne-Lise Ruellan[1], Clotilde Allavena[2], Francesco Salvo[3], Gwenaelle Veyrac[4]

[1]) Regional Center of Pharmacovigilance, Clinical Pharmacology department, University Hospital, Nantes, France. [2]Department of tropical and infectious diseases. University Hospital, Nantes, France. [3]) Regional Center of Pharmacovigilance, Clinical Pharmacology department, University Hospital Center, Bordeaux, France. [4]) Regional Center of Pharmacovigilance, Clinical Pharmacology department, University Hospital Center, Nantes, France

Introduction: Since December 2021, an association with rilpivirine (RPV) and cabotegravir (CAB),is marketed for the treatment of HIV infection, having obtained its European marketing authorization in December 2020. These long-acting (LA) ARV therapy (ART)) is recommended to people with HIV on stable ART for at least 6 months, and $\geq$ 200 CD4/mm3, and no evidence of current or previous mutation resistance and no history of virological failure to non nucleoside reverse transcriptase inhibitor (NNRTIs). Lenacapavir (LEN), the first capsid in patients with multidrug-resistant HIV-1 infection for whom available ART do not achieve virological suppression, is on the market since December 2022.
Aim/Objective: To identify the main post-marketing adverse drug reactions (ADR) associated with LA injectable ART in the French Pharmacovigilance database (FPVD).
Methods: Adverse drug reactions (ADRs) were collected on all spontaneous reports and according to serious and non serious cases, notified to the FPVD until the 22th of March, 2024 when RPV or CAB or LEN were considered as suspected drugs. According to the System Organ Class (SOC), MedDRA, ADRs were classified according the most SOC identified for the RPV/CAB association, RPV alone, CAB alone or LEN alone. We have also looked at the cases collected in the international Pharmacovigilance database (Vigibase®), in order to match the data obtained. ADRs reported by manufacturers or observed during clinical trials were not included in the analyse.
Results: 57 cases of ADRs were collected after case-by-case analysis : 46 cases with RPV and CAB; 6 cases with RPV and 4 cases with CAB, and 1 case with LEN. Overall, median age of patients was 47 year-old [min 23- max 68], male/female ratio was 1.9. The most frequent reported ADRs (SOC) were general disorders and injection site reaction (n = 26), psychiatric disorders (n = 12), musculoskeletal and connective tissue disorders (n = 11). 29 reports (50.9%) were considered serious including psychiatric disorders (n = 3) such as anxiety or depression, vascular disorders (n = 2) as hematomas or deep-vein thrombosis, or infections (n = 6) such as abscesses at the site of administration.
Conclusion: In this national retrospective analysis, the collected data seem similar to the international Pharmacovigilance database (Vigibase®) for the more frequent SOC. The severity of the reported cases should be taken into consideration, representing more than 50% of the selected cases. Healthcare professionnals must remain vigilant regarding the severity of reported effects, although LA treatment remains a therapeutic option of interest for eligible patients.

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Melatonin Safety Profile in the Neuropsychiatric Pediatric Setting—A Retrospective Global Study

Rita Avó-Baião[1,2], Luísa Prada[1,2], João Paulo Fernandes[3], Márcia Silva[3]

[1]Clinical Pharmacology and Therapeutics Laboratory, Faculty of Medicine, University of Lisbon, Lisbon, Portugal. [2]Local Health Unit Santa Maria, Lisbon, Portugal. [3]INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon, Portugal

Introduction: Melatonin is increasingly used in pediatric populations, be it prescribed or dispensed as over the counter (OTC) (1) yet comprehensive insights into adverse drug reactions (ADRs) from local or global data remain limited. This study describes the landscape of melatonin-associated events in pediatric patients in VigiBase, the World Health Organization-Uppsala Monitoring Centre database of reports of suspected ADR.
Aim/Objective: To assess and characterize the safety profile of this medicinal product in the pediatric population, on a global level.
Methods: Individual Case Safety Reports (ICSRs) for individuals aged 0-17 years containing melatonin ADRs in VigiBase were extracted for the period from 2000 to 2023. Descriptive statistics characterized demographics and reporting trends were examined over time, and subgroup analyses by age, MedDRA System Organ Class (SOC) and Preferred Terms (PT).
Results: A total of 975 ICSR for suspected melatonin ADR in pediatric age group were obtained, with the majority distributed among the age ranges of 2-11 years (48.7%) and 12-17 years old (47.9%). The majority of reactions were categorized within the SOC of "Psychiatric disorders" in 43.5% of ICSRs identified, with the most reported PT being "Intentional overdose" (10.4%), followed by "Aggression" (7.6%). Regarding co-reported drugs, methylphenidate was the most representative, reported as both a suspect/interacting drug (5.6%) and a concomitant drug (5.1%), indicating melatonin's potential safety issues and its prevalent use for sleep disorders in pediatric patients with comorbid neuro-psychiatric disorders. Of the total reports, 375 (38.4%) had melatonin as the only suspect medicine, with the most reported PT being "Aggression" (42 ICSRs).

The majority (53.3%) of reports were submitted in the last four years of the study time analysis.

Conclusion: This global study provides valuable insights into melatonin related ADRs in the pediatric population, revealing an attention-worthy increasing trend. Multiple studies (2–4) have already raised the question of there being an association between melatonin and aggression, but none have yet definitively clarified whether this relationship is causal or the result of reverse causality. However, it is essential to acknowledge the study's limitation in not encompassing the total world of melatonin supplements dispensed as OTC or sold online but not reported to pharmacovigilance systems, due to national level legislations. Considering the popularity of this product and its accessibility, this topic deserves public health authorities' attention for its possible future impact.

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Targeted Pharmacovigilance for Metronidazole-Induced Neuropathy in Patients of Amoebic Liver Abscess at A Tertiary Care Hospital: An Ambispective Study

MD Gulam Gouse[1], Puneet Dhamija[2], Shazia Hasan[2], Bhupinder Solanki[2], Intezar Ahmed[2], Rohit Gupta[2], Ravi Kant[2], Farhan-ul Huda[2]

[1]Department of Pharmacology, School of Pharmaceutical Sciences and Technology, Sardar Bhagwan Singh University, Dehradun, India. [2]All India Institute of Medical Sciences, Rishikesh, India

Introduction: Metronidazole has been the front-line choice for several anaerobic and protozoan infections worldwide (1). Metronidazole is widely prescribed and recognized for its effectiveness in treating various infections, including amoebic liver abscesses (ALA). However, its use comes with potential complications, particularly the development of neuropathy, which affects the nerves and can cause significant discomfort and impairment for patients (2). While existing knowledge suggests that neuropathy is a rare side effect, the exact incidence rates and risk factors remain areas of ongoing research. Our study addresses the neuropathy risk associated with metronidazole treatment for ALA.

Aim/Objective: To assess the incidence and severity of metronidazole-induced neuropathy in patients with ALA managed with Metronidazole.

Methods: It was an observational study conducted in the Department of General Medicine, General Surgery, Gastro-Enterology, Paediatric Surgery and Pharmacology, All India Institute of Medical Sciences, Rishikesh, UK, India. The duration of the study was six months. All patients diagnosed with ALA managed with Metronidazole were included (Adult and paediatric above 5 years and patients from both genders). The suspected adverse drug reaction reporting form, version 1.4, was used to collect data. All the suspected cases of adverse events were reported to the ADR Monitoring Centre, AIIMS, Rishikesh. The causal relationship was established by the standardized WHO UMC Causality Assessment. The analyzed data was then uploaded to Vigiflow software and sent to the National Co-ordination Centre.

Results: A total of 165 patients were recruited. 23 developed neuropathies, primarily due to long-term medication use and risk factors like alcohol, tobacco, and diabetes. Most affected were males (69%) within the 20-50 age range. The occurrence of neuropathy symptoms was most frequently reported with the 800 mg dose. The most common duration of Metronidazole use was 30 days. 26% of patients suffered from severe symptoms of metronidazole-induced neuropathy.

Conclusion: This study identified the percentage of patients developing neuropathy after metronidazole use in ALA, including gender, age, severity, dose, and duration of treatment. Awareness of the drug's potential for neurotoxic effects is crucial, and its use should be judiciously managed to prevent unnecessary exposure. These data will be helpful for the risk minimization and risk management plans.

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Pregnancy Outcomes in Females Living with Cystic Fibrosis Exposed to CFTR Modulators: Early Findings from a French Nationwide Cohort Study

Laurent Chouchana[1], Mathis Collier[1], Jean-Marc Treluyer[2]

[1]Assistance Publique - Hopitaux de Paris, Paris, France. [2]Université Paris Cité, Paris, France

Introduction: Recent therapeutic advances, mainly with the combotherapy of CFTR modulators elexacaftor/tezacaftor/ivacaftor (ETI), have dramatically improved life expectancy of people living with cystic fibrosis. Consequently, female living with cystic fibrosis (fwCF) are living through their reproductive years and the rate of pregnancies under CTFR modulators is rapidly increasing. Due to tremendous benefits for the women, these treatments are generally followed-on through pregnancy, although data regarding their safety for the fetus are scarce to date.

Aim/Objective: This study aimed to assess pregnancy outcomes in fwCF exposed to CFTR modulators.

Methods: We performed a nationwide cohort study based on the French health insurance data warehouse (SNDS). All singleton pregnancies lasting more than 22 weeks of gestation (WG) and linked with offspring data from January 2018 through August 2023 were included. fwCF were identified through hospital discharge diagnosis and long-term disease codes. Exposure to CFTR modulators during pregnancy was defined as at least one filled prescription during the 30 days before pregnancy and up to delivery. Major birth defects were assessed up to three months of life using EUROCAT classification.

Results: Of 3,656,198 pregnancies during study period, 560 occurred in fwCF, including 125 exposed to CFTR modulators, mostly ETI (114 being exposed during first trimester and 101 being exposed during whole pregnancy). Among pregnancies in fwCF, women exposed to CFTR modulators had markers for a most severe CF history. Pregnancy outcome was exclusively livebirth (n = 124, 99%), except medical termination of pregnancy (without details) in one case. The rates of preterm birth (20.2% vs. 18.1%; p = 0.7) and of major birth defects (4.0% vs 4.4%; p = 1.0) was similar in exposed pregnancies compared to unexposed. Small for gestational age was

significantly less frequent in exposed pregnancies compared to unexposed (7.3% vs 17.4%; p = 0.008).
Conclusion: Our study provides reassuring early findings on the use of CFTR modulators in pregnant fwCF. Furthermore, the lesser rate of small for gestational age in pregnancies exposed to CFTR modulators might reflect a better fetal development under treatment. Ongoing surveillance is necessary to confirm these findings.
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Viability of Serious Gaming in Effective Risk Minimization

Marie Liles-Burden, Carmit Strauss

Takeda Development Centers Americas Inc., Cambridge, USA

Introduction: Risk minimization activities are interventions intended to prevent or reduce the occurrence or severity of an adverse reaction [1]. In instances where routine risk minimization is not sufficient, an additional risk minimization measure may be required [1]. While current regulatory climate seems to accept digital component to an aRMM, little innovation has occurred in the delivery of RMMs. Game-based learning in the form of serious gaming and/or gamification-based interventions have been successfully implemented in patient and prescriber education [2, 3]. However, there is little information of its use in aRMM design.
Aim/Objective: Present an argument for the use of game-based learning interventions in aRMM design.
Methods: A literature search utilizing various databases (e.g., EmBase, Ovid, Biosis Previews, and Medline) was conducted gaming terminology such as game-based learning, serious gaming, and gamification in patient and prescriber education to identify overall viability of game-based learning. A second search of gaming terminology paired with risk minimization terminology such as additional risk minimization measures, risk evaluation and mitigation strategies, and corresponding acronyms was conducted using the same databases to identify current application of gaming in risk minimization activities. Results of both were evaluated against regulatory guidelines such as the Good Pharmacovigilance Practices (GVP) Module XVI rev 2 [1] and draft rev 3 [4] and commentary regarding aRMMs to evaluate viability.
Results: While there were no literature results regarding practical application of gaming in risk minimization activities, results identified over 700 articles of gamification in patient and prescriber education. Major themes among the articles ranged from overall design considerations to effectiveness of game-based learning experiences among various interventions and learning spheres. There are challenges in the utilization of gamification including the need for design guidelines for multi-media resources such as gamification interventions (CIOMS XI) [5], ineffective design models, and waning engagement over time. However, when evaluated against GVP Module XVI, game-based interventions aligned with several key principles for aRMMs including patient centricity, digital application, portability and accessibility of information, ease and speed of evaluating effectiveness in a timely manner.
Conclusion: In conclusion, aRMM gamification provide a unique opportunity for innovation in creating engaging and effective aRMMs. The interactive nature of game-based learning enables real-time feedback loop for material content adjustments based on responses. New levels with new concepts can be added to increase engagement or measure retention. Additional research including practical examples in this space are needed.
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The Top Reported Medications Associated with Life-Threatening Adverse Drug Events in Saudi Arabia: Insights from a Spontaneous Reporting System

Fotoun Alblowi, Muhanad Alharbi, Alhanouf Aldajani

saudi food and drug authority, Riyadh, Saudi Arabia

Introduction: Adverse drug events (ADEs) refer to undesirable experiences associated with the use of a medicinal product [(1)]. While most ADEs are relatively mild and manageable, there are instances where these events can escalate to life-threatening incidents. Life-threatening ADEs are characterized by severe and potentially fatal outcomes, requiring immediate medical attention and intervention. The majority of these incidents are preventable [(2)].
Aim/Objective: To measure the rate and percentage of ADEs and associated medications leading to life-threatening situations in Saudi Arabia using data from the Saudi Vigilance spontaneous reporting system.
Methods: A retrospective analysis was conducted using the Saudi Vigilance spontaneous reporting system over a 12-month period. It included all cases reported by healthcare providers that resulted in life-threatening incidents from January to December 2023. Reports that did not involve life-threatening incidents, reports from the public or pharmaceutical companies, and adverse drug events (ADEs) not reported during the study period were excluded. Adverse drug reactions (ADRs) were coded using the MedDRA® coding system. Descriptive statistics were used to analyze the data, and the results were presented as percentages of the five most frequently reported medications and associated life-threatening events, as well as the age group and gender of the patients in these reports.
Results: A total of 267,953 reported adverse drug reactions (ADRs) were examined, and among them, 357 reports (0.1%) met the inclusion criteria for life-threatening incidents. Of these reports, the majority involved males, totaling 190 (53%), while the remaining reports were related to females, 167 (47%). Furthermore, the highest percentage of reports pertained to elderly patients (36.7%), followed by adults (33.6%), with a smaller percentage involving pediatric patients (8%), and the remaining cases were unspecified.
Regarding the medications most frequently associated with life-threatening situations, Insulin accounted for 14.8% of the reports and was primarily linked to hypoglycemia (52 reports, 14.6%). Warfarin

was the second most commonly reported medication, representing 9.2% of the reports, with an increased International Normalized Ratio (INR) leading to bleeding being the predominant associated adverse drug event (41 reports, 11.4%). Among the antibiotic reports, Vancomycin (5%), Ceftriaxone (4.2%), and Amoxicillin (3.1%) accounted for a total of 12.3% of the reports, mainly associated with allergic reactions, including anaphylaxis (42 reports, 11.8%).

Conclusion: Although the occurrence of life-threatening adverse drug events (ADEs) is relatively rare, it is imperative to prioritize the implementation of absolute safeguards and risk minimization strategies in order to enhance medication safety. To effectively work towards this objective, it is recommended to raise awareness about medications frequently associated with life-threatening incidents and to conduct targeted research investigations that examine the specific correlation between certain drugs and life-threatening events.

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Association Between Neurodevelopmental Disorders Reporting in Offspring and Antidepressant Use During Pregnancy

Laure-Hélène Préta[1], Naïm Bouazza[2], Jean-Marc Treluyer[2], Laurent Chouchana[1]

[1]Assistance Publique - Hopitaux de Paris, Paris, France. [2]Université Paris Cité, Paris, France

Introduction: Antidepressant may be required for treating depression during pregnancy as it affects 7% to 13% of pregnant women [1]. Literature is conflicting regarding the risk of neurodevelopmental disorders (NDD) in offspring associated with in utero exposure to antidepressants and the role of underlying disease.

Aim/Objective: To assess the association between NDD reporting and the use of antidepressant during pregnancy.

Methods: We analyzed safety reports related to pregnancy in VigiBase, the WHO global safety database from 2000 to 2020. To identify NDD cases, we selected the relevant MedDRA Preferred Terms. To assess an association between antidepressant (ATC N06A) use during pregnancy and NDD reporting in offspring, we performed several disproportionality analyses by calculating adjusted reporting odds ratios (aROR) in a case/non-case multivariate model, according to the type of antidepressant and the type of NDD.

Results: Of 171,652 safety reports, we identified 1,133 NDD cases, including 324 cases exposed to antidepressants, mainly fluoxetine (n = 114; 35%) and paroxetine (n = 87; 27%). The most common type of NDD reported with antidepressants was autism spectrum disorder (n = 196; 60%). Overall, antidepressant use during pregnancy was associated with an increased reporting of NDD compared to the use of other psychotropic drugs (aROR 3.7; 95% CI 2.9-4.8). When comparing to SNRIs, NDD reporting was significantly increased with SSRIs (aROR 2.4 95% CI 1.7-3.3). Especially, comparison between agents showed that NDD are disproportionately reported for paroxetine (aROR 2.0; 95% CI 1.5-2.6) and fluoxetine (aROR 4.6; 95% CI 3.6-5.9) compared to other psychotropic drugs. In contrast, RORs were not significant for sertraline, escitalopram and citalopram. Results were consistent across sensitivity analyses.

Conclusion: Based on global safety data, our study found an increased reporting of NDD, mainly autism spectrum disorders, associated with SSRIs use during pregnancy. At a drug level, increased reporting was found with fluoxetine and paroxetine, but not with sertraline, escitalopram and citalopram. Further studies must be conducted to assess this potential risk. In offsprings of pregnant women exposed to antidepressants, pediatricians should seek for NDD to perform early diagnosis if appropriate.

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Impact of Mandatory Report on Adverse Event Declaration in an Academic Tertiary Center of Quebec

Maude Lavallée[1,2], Sonia Corbin[1,2], Pallavi Pradhan[3,2], Laura Blonde Guefack Djiokeng[3,2], Magalie Thibault[2], Julie Méthot[1,2], Anick Bérard[4,5], Marie-Eve Piché[6,2], Fernanda Raphael Escobar Gimenes[7], Rosalie Darveau[8], Isabelle Cloutier[1,8], Jacinthe Leclerc[1,2]

[1]Université Laval, Faculty of Pharmacy, Quebec, Canada. [2]Centre de recherche, Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval, Quebec, Canada. [3]Université du Québec à Trois-Rivières, Anatomy department, Trois-Rivières, Canada. [4]Centre de recherche du Centre Hospitalier Universitaire Ste-Justine, Montreal, Canada. [5]Université de Montréal, Faculty of Pharmacy, Montreal, Canada. [6]Université Laval, Faculty of Medicine, Quebec, Canada. [7]University of São Paulo, Faculty of Nursing, Sao Paulo, Brazil. [8]Institut universitaire de cardiologie et de pneumologie de Québec–Laval University, Quebec, Canada

Introduction: Underreporting adverse event (AE) is a worldwide problem since many years.[1] Different countries have implemented legislation to regulatereporting and seek to improve drug safety in post-marketed phase.[2-4] In 2019, Canada adopted Vanessa Law, making it mandatory for hospitals to report serious AE (SAE) that occur in their establishment within 30 days.[5]

Aim/Objective: 1) To document the incidence of AE and SAE over time in a "real" clinical context, 2) To quantify SAE reported to Health Canada among those that have occurred, and 3) To assess the Vanessa's Law impact in SAE reporting to Health Canada

Methods: 500 randomly selected electronic medical records (EMR) from 2018 to 2021were scrutinized retrospectively to identify AE and their reporting by our teams. Patients were hospitalised at Institut Universitaire de cardiologie et de pneumologie de Québec–Université Laval between 2018 to2021. Descriptive (median, min-max, interquartile range and proportion) and comparative analyses were performed. Incidence rates of AE and SAE and stratifications were also performed.

Results: Among the 500 patients, 9568 drug products were consumed, corresponding to 2541 AE, including 302 SAE. Almost 44% were women; patients had median of 4 comorbidities [min :1- max: 12], with youngest patient being 21 years old and the oldest 96 years old (median: 69 years old). Majority of the patient didn't experiment any SAE (median: 0, [0-10]). Rate of AE was higher in 2018 (5.40 per person-year) and lower in 2021 (4.54 per person-year). Spearman's rho revealed a correlation between the number of AE/patient and the number of comorbidities ($r = 0.117$; $p = 0.009$), the number of drugs products consumed ($r = 0.578$; $p < 0.001$), and the length of hospital stay ($r = 0.629$; $p < 0.001$). No SAE was found as declared in EMR corresponding to a proportion of 0%.

Conclusion: No declaration was found in the 500 EMR studied. However, an internal registry was found a posteriori and showed that 76 SAE were reported to Health Canada. None of those 76 were included in the 302 SAE identified by our teams. Considering the limited impact of the new legislation (i.e 76 SAE reports in 64 000 hospitalisations), other solutions need to be explored to improve reporting. Investigating the knowledge and perception of healthcare professionals would surely be a good avenue to better understand the underreporting issue in Canada.

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Prenatal Exposure to Proton Pump Inhibitors and Risk of Serious Infections in Offspring: A Nationwide Cohort Study

Mylène Tisseyre[1], Mathis Collier[1], Nathanael Beeker[1], Florentia Kaguelidou[2], Jean-Marc Treluyer[2], Laurent Chouchana[1]

[1]Assistance Publique - Hopitaux de Paris, Paris, France. [2]Université Paris Cité, Paris, France

Introduction: Proton Pump Inhibitors (PPIs) use in children inscreases the risk of infections, prompting investigation into the impact of prenatal PPI exposure on serious infections in offspring. Despite the burden posed by early-life infections and emerging evidence, a research gap persists in understanding this association.

Aim/Objective: To assess the association between prenatal PPI exposure and serious infections in full-term infants during their first year of life.

Methods: Using the French health insurance data warehouse (SNDS) between 2013 and 2018, we conducted a retrospective population-based cohort study on singleton, full-term liveborn non-immunocompromised infants, stratified according to PPI use in early life during the first three months. PPI dispensing in ambulatory care settings during pregnancy defined the exposure. Outcomes concerned any serious infections in offspring between 3 and 12 months of age, excluding maternal-origin infections during the first three months of life. Adjusted Odds Ratios (aORs) were estimated using logistic regression with multivariable models to control for potential confounders.

Results: Out of the 2,485,545 infants included, 497,060 (23.3%) were prenatally exposed to PPI and 97,767 (4.6%) used PPI in early life. Main infections were pulmonary and gastrointestinal infections. Prenatal exposure to PPI was associated with serious infections in offspring (aOR, 1.09 (95% CI, 1.07–1.10) for infants without PPI use in early life. Conversely, no association was found for infants with PPI use in early life (aOR, 1.05 (95% CI, 1.00–1.11). Similar associations emerged regarding timing of exposure during pregnancy, various infections sites, and types. Gastrointestinal infections were the sole site with persistent significance in all models.

Conclusion: Prenatal exposure to PPI is common and is not associated with a major risk of serious infections in infants during their first year of life. However, even after adjusting for several confounding factors, we cannot rule out a weak association, particularly among infants who did not use PPI in early life. Considering these results comprehensively, the use of PPI during pregnancy may offer reassurance while emphasizing the importance of adheringto clinical guidelines.

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Pharmacy Survey in the City of Saida: Pharmaceutical Waste Management

Yassine Aimer[1,2], Ikram Asmaa Mokadem[3], Mounia Guettaf[3], Omar Benali[4,2]

[1]Process Engineering Department, Faculty of Technology, University Of Saida Dr Moulay Tahar, Saida, Algeria. [2]Laboratoire de Chimie: Synthèse, Propriétés et Applications, University of Saida Dr Moulay Tahar, Saida, Algeria. [3]Process Engineering Departement, Faculty of Technology, University Of Saida Dr Moulay Tahar, Saida, Algeria. [4]Chemistry Department, Faculty of Sciences, University Of Saida Dr Moulay Tahar, Saida, Algeria

Introduction: The management of various types of waste, particularly pharmaceutical waste, has always been regulated and considered to protect the environment and public health [1]. Worldwide, the management of waste medicines and pharmaceuticals, which are deemed hazardous waste, is becoming a concern in the health sector. In Algeria, significant improvements and mutual support among various sectors (including local authorities, environmental agencies, public health institutions), in collaboration with civil society, are necessary to find appropriate solutions to this issue and implement a national strategy for sustainable development [2].

Aim/Objective: The city of Saida, like other cities in Algeria, has experienced significant growth over the last few decades due to several factors: demographic development, high demand for necessities and improved quality of life, particularly in healthcare, which has led to a considerable increase in the consumption of pharmaceutical products. This has resulted in the generation of large quantities of waste, much of which is hazardous and detrimental to the environment. In this context, a survey was conducted on the management of this waste in pharmacies within the city of Saida.

Methods: We employed exhaustive sampling by approaching 38 practicing pharmacists during the period from May to June 2021. The questionnaire consisted of three sections: one pertaining to the pharmacist's awareness of pharmaceutical waste management, another focusing on their practices and methods for managing expired medicines within their pharmacy, and a final section concerning their perspectives on the future of waste management in addition to their expectations and proposals in this area.

Results: The results revealed that the majority of pharmacists are aware of waste management practices, but 60% are unaware of the national law. While 55% are knowledgeable about waste classification and sorting within their pharmacies, three-quarters admit to not having participated in any training courses on pharmaceutical waste management. Seventy percent are familiar with various waste

treatment processes, particularly incineration. Over 60% of pharmacists remove products from shelves 30 days prior to expiration, with storage periods ranging from 1 to several years. On average, pharmacies generate 56 kg/year of waste, and all pharmacists use cardboard boxes for waste storage. Moreover, more than 60% segregate waste based on its galenic form.

Conclusion: After these findings, we can conclude that pharmaceutical waste management in the city of Saida, particularly at the level of pharmacies, needs improvement and optimization based on these recommendations:

- Support pharmacists with regular training to ensure safe management of pharmaceutical waste.
- Encourage young entrepreneurs in waste treatment businesses with comprehensive training.
- Collaborate with civil society to develop a national strategy for sustainable waste management, involving awareness campaigns and training programs.

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Partnerships and Pharmacovigilance Agreements Regulations in Latin America

Sandra Tatiana Mendoza Arenas, Alejandra Cruz

ICON, Bogota, Colombia

Introduction: Operation of Marketing Authorization Holders (MAH) is supported by stakeholders such as business partners, wholesalers, distributors, retailers, subcontractors and vendors. MAH may transfer some or all of the obligations and functions to these third parties but not the accountability in Pharmacovigilance (PV)[1]. Therefore, PV activities or safety data exchange must be documented in Pharmacovigilance agreements (PVA).

Aim/Objective: Identify if Partnerships and PVAs are regulated by the Health Authorities (HA) in Latin America.

Methods: Authors selected 18 countries in Latin America in which they have previous experience, reviewing legislation of 16 HA located in their websites. Honduras (not PV legislation) and Nicaragua (website unavailable during the review) were excluded.

Results: 9 countries (Argentina, Brazil, Chile, Costa Rica, Cuba, Equator, Panama, Peru, Venezuela) indicate that a contract has to be in place with stakeholders which outsource PV activities[2,3,4,5,6,7,8,9,10]. Cuba indicates that PVA is also required when distribution and manufacture or licensing, promotion and marketing is performed by third parties[8].

- Outsourcing in PV must be notified to HA in Chile, Costa Rica, Peru, Venezuela[4,6,9,10].
- HA in Brazil, Chile, Costa Rica, Panama, Peru indicate that stakeholders will be subject of inspection. Panama consider PV outsourcing is a factor to plan an inspection[3,4,6,7,10].
- Argentina, Brazil, Costa Rica, Cuba, Peru state that PV accountability remain with MAH[2,3,6,8,10].
- Legislation in Argentina, Chile indicate that MAH should assess capabilities of stakeholders and monitor timely gap resolution to mitigate risks[2,4].

1 country (Colombia) has a draft guide which indicates that MAH must notify HA if AE report is outsourced, providing responsibilities, accountability is not transferred, stakeholder is subject to inspection.

6 countries (Bolivia, El Salvador, Guatemala, Mexico, Paraguay, Uruguay) do not refer to PVA.

Conclusion: Most of HA make reference to stakeholders that perform PV activities but not to other third parties that may be aware of AE when performing the service contracted as they have interaction with patients and healthcare professionals. None provide guidance about development and execution of PVA.

MAH have many challenges to put PVA in place: some stakeholders are not aware or do not understand its relevance, negotiation is time-demanding, PV language seems complex, etc. Nevertheless, PVA in partnerships are an essential component of the PV system; not having them to govern and manage PV activities and safety information exchange is a risk for MAH impacting regulatory responsibilities, patient safety, and reputation. In consequence, it is suggested that HA guide MAH in the development and execution of PVA.

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Automating Population-Based Studies for 30-Day Adverse Drug Event Detection in Older Adults with Chronic Kidney Disease Using High-Throughput Computing

Sheikh Abdullah[1,2], Neda Rostamzadeh[1,2], Fatemeh Ahmadi[1,2], Flory T Muanda[1,2,3], Amit Garg[1,2,3]

[1]Western University, London, Canada. [2]ICES Western, London, Canada. [3]Lawson Health Research Institute, London Health Sciences Centre, London, Canada

Introduction: Safety issues are detected in about one-third of prescription drugs in the years following regulatory agency approval (1). Older adults with chronic kidney disease are at particular risk of adverse reactions to prescription drugs.

Aim/Objective: To use high-throughput computing and automation to conduct 700+ drug-safety cohort studies in older adults in Ontario, Canada.
Methods: The studies were population-based, new-user cohort studies conducted using linked administrative health care databases in Ontario, Canada (January 1, 2008, to March 1, 2020). Individuals aged 66 years or older with a baseline estimated glomerular filtration rate (eGFR) measurement within 12 months before the cohort entry who filled at least one outpatient prescription through the Ontario Drug Benefit program were included. We identified 3.2 million older adults in the source population during the study period and built 700+ medication cohorts, each containing mutually exclusive groups of new users and nonusers. Nonusers were randomly assigned cohort entry dates that followed the same distribution of prescription start dates as new users. New users and nonusers were balanced on ~400 baseline health characteristics using inverse probability of treatment weighting on propensity scores within 3 strata of baseline eGFR: ≥60, 45 to < 60, < 45 mL/min per 1.73 m2. We compared new user and nonuser groups on 74 clinically relevant outcomes in the 30 days after cohort entry. In each cohort, eGFR-stratum-specific weighted risk ratios and risk differences were obtained using modified Poisson regression and binomial regression, respectively. Additive and multiplicative interactions by eGFR category were examined. Drug-outcome associations that met pre-specified criteria (identified signals) will be further examined in additional analyses and visualizations.
Results: The initial medication cohorts had a median of 6120 new users per cohort (IQR: 1469-38 839) and a median of 1 088 301 nonusers (IQR: 751 697-1 267 009). Medications with the largest number of new users were amoxicillin trihydrate (n = 1 000 032), cephalexin (n = 571 566), prescription acetaminophen (n = 571 563), and ciprofloxacin (n = 504,374); 19% to 29% of new users in these cohorts had an eGFR < 60. We found a significant increase in 368 exposure-outcome associations as kidney function declined. Antibiotics (macrolides and cephalosporins), SSRIs, and benzodiazepines, were linked with the most associations. clarithromycin (22) and baclofen (17) were the most frequently associated medications with ADR.
Conclusion: This accelerated approach to conducting postmarket drug-safety studies has the potential to more efficiently detect drug-safety signals in a vulnerable population.
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Sudden Sensorineural Hearing Loss After mRNA COVID-19 Vaccination: Early Safety Signal Generation Using Disproportionality Analysis on a Nationwide Pharmacovigilance Database

Dalil Boulefaa[1], Francesco Salvo[2], Marie-Blanche Rabier[3], Hélène Geniaux[4], Marion Lepelley[5], Fanny Rocher[6], Julien Mahe[7], Aurélie Grandvillemuin[8], Hung Thai-Van[9,10,11], Haleh Bagheri[1]

[1]Department of Medical and Clinical Pharmacology, Regional Pharmacovigilance Center of Toulouse, Clinical Investigation Center 1436, Toulouse University Hospital, Toulouse, France. [2]Department of Medical Pharmacology, Hospital Univeristy of Bordeaux, Inserm, BPH, U1219, Equipe AHeaD, Bordeaux, France. [3]Regional Pharmacovigilance Center of Franche-Comté, Besançon University Hospital, Besançon, France. [4]Regional Center of Pharmacovigilance of Limoges, Limoges University Hospital, Limoges, France. [5]Regional Center of Pharmacovigilance of Grenoble, Grenoble-Alpes University Hospital, Grenoble, France. [6]Department of Pharmacology and Pharmacovigilance Center, Côte d'Azur University Medical Center, Nice, France. [7]Department of clinical Pharmacology, Regional Pharmacovigilance Center, Poitiers University Hospital, Poitiers, France. [8]Regional Center of Pharmacovigilance of Bourgogne, Dijon University Hospital, Dijon, France. [9]Service d'Audiologie & d'Explorations Otoneurologiques, Hospices Civils de Lyon, Lyon, France. [10]10. Claude Bernard Lyon 1 University, Villeurbanne, France. [11]Institut Pasteur, Institut de l'Audition, Paris, France

Introduction: Sudden sensorineural hearing loss (SSNHL) has been reported for mRNA COVID-19 vaccines. Our previous pharmacovigilance study suggested a causal relationship between SSNHL and mRNA vaccines [1]. However, the results of pharmaco-epidemiological investigations are controversial [2-4].
Aim/Objective: The aim of our study was to assess the safety signal generation in the early phases of the COVID-19 vaccination campaign, using a disproportionality analysis by estimation of reporting Odds ratio (ROR). Secondly, we analysed all cases of SSNHL reports between February 2022 and February 2023 - first and second vaccine booster campaigns in France.
Methods: Data from 1st January 2011 to 31st January 2022 were extracted from the French pharmacovigilance data base (FPVDB). Cases were all spontaneous reporting of adverse event following immunisation (AEFI) for elasomeran (Spikevax®) and tozinameran (Comirnaty®), while non-case were AEFI reported for all other vaccines (excluding other COVID vaccines). The index reports were "hearing impairment" and the reference reports were all other reports. Disproportionality analysis was performed on a monthly basis over 2021. Four methods were assessed, using a standard methodology as a reference, adjusting for age, sex and exposure to ototoxic drugs (OD), excluding reference reports of AEFI commonly reported for vaccines (RRPT5), and a pooled multivariate analysis adjusted for sex, age, OD and excluding RRPT5. Furthermore, we reviewed suspected cases of SSNHL occurring after vaccination with mRNA COVID-19 vaccines reported in France during COVID-19 booster campaigns, based on a comprehensive medical evaluation including patient medical history, side, and extent of hearing loss.
Results: Using a standard methodology, we identified a signal in July 31st, 2021 (ROR = 1.50, CI95% [1.06 - 2.18]). The most effective approach to early signal detection was to exclude RRPT5 and adjustment for gender, age and OD. This approach helped to spot the hearing impairment signal as early as March 31st, 2021 (ROR = 2.67, CI95% [1.36–5.57]). The reporting rate for SSNHL between February 2022 and February 2023 was 0.83/1,000,000 doses for tozinameran and 4.3/1,000,000 for elasomeran. One case of positive rechallenge was reported for tozinameran, suggesting the strong likelihood of a causal relationship.
Conclusion: SSNHL occurring after mRNA COVID-19 vaccines are a very rare, and do not call into question their benefits. Our data suggested a higher reporting rate of hearing impairment with mRNA COVID-19 vaccines compared to other vaccines. The use of a well-designed disproportionality analysis could be an added value to highlight a safety signal earlier in the 2021 vaccination campaign.
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Intravitreal Vascular Endothelial Growth Factor Inhibitors and Cardiovascular Adverse Drug Reactions: Results of the French Pharmacovigilance Survey

Aurélie Bobet[1], Leila Chebane[1], Annie-Pierre Jonville[2], Marina Babin[3], Thomas Soeira[4], Haleh Bagheri[1]

[1]Regional Pharmacovigilance Center Of Toulouse, Department Of Medical And Clinical Pharmacology, Toulouse, France. [2], Regional Pharmacovigilance Center of Centre Val De Loire, Department Of Medical And Clinical Pharmacology, Tours, France. [3]3. Regional Pharmacovigilance Center Of Angers, Angers University Hospital, Angers, France. [4]4. Regional Pharmacovigilance Center Of Marseille, Department Of Medical And Clinical Pharmacology, Marseille, France

Introduction: Age-related macular degeneration is a degenerative disease of the macula. The treatment is based on intravitreal Vascular Endothelial Growth Factor inhibitor (VEGF-I). VEGF and other factors act as powerful mitogenic and chemotactic factors, promoting vascular permeability. When administered systemically, they are associated with thromboembolic events and arterial hypertension. Data of literature remain controversial concerning the occurrence of cardiovascular Adverse Drug Reactions (ADRs) with VEGF-I [1-3].
Aim/Objective: The objective was to assess the risk of cardiovascular ADRs associated with the use of VEGF-I.
Methods: The survey was required by ANSM (Agence Nationale de Sécurité du Médicament). We carried out a retrospective study from the date of marketing of ranibizumab, aflibercept and bevacizumab to 06/30/2023, based on extraction from the French PharmacoVigilance Database and pharmaceutical laboratory.
Results: A total of 127 cases were selected (ranibizumab n = 83, aflibercept n = 37, bevacizumab n = 7).
Twenty one cases of arterial hypertension were selected (ranibizumab n = 13, aflibercept n = 6, bevacizumab n = 1). The median age was 81 years (women: 71%). The median delay to onset was 8.5 days [1 - 31].

A total of 108 thromboembolic events were analyzed (ranibizumab n = 68, aflibercept n = 32, n = 6 bevacizumab), including stroke (60.4%), transient ischemic attack (13.2%), myocardial infarction (7.5%), pulmonary embolism (5.7%), ocular arterial or venous occlusion (5.7%), cerebral thrombosis (2.8%), deep or superficial vein thrombosis (2.8%) and angina attack (1.9%). The median age was 81 years (women: 56.6%). The median delay to onset was 9 days [1 - 119].

Cardiovascular and thromboembolic risk factors found were: arterial hypertension (35.2%), dyslipidemia (17.6%), diabetes (14%), smoking (10.2%), neoplasia (10.2%), autoimmune diseases (3.7%), obesity (3.7%), alcoholism (2.7%) and history of thrombotic events (2.7%).

For 6 cases, we had information regarding the readministration of the I-VEGF after the ADRs. We had 2 positive rechallenges and 4 negative rechallenges of the ADR.
Conclusion: Our data suggest a potential risk of occurrence of cardiovascular ADRs after VEGF-I exposure. The Summary of Product Characteristics of these drugs remain poorly information and only indicate a theoretical risk. Health professionals should be aware of cardiovascular ADRs, especially in patients of high risk.

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Frozen Shoulder After COVID-19 Vaccination : A Review of covid-19 Vaccines Surveillance in France

Ophélie Brachet[1], Noémie Giffard[1], Pierre Gillet[2], Haleh Bagheri[3], Francesco Salvo[4], Joelle Micallef[5], Martine Tebacher-Alt[6], Sophie Gautier[7], Valérie Gras-Champel[8], Nathalie Massy[9], Marie-Blanche Valnet-Rabier[10], Guillaume Drablier[1], Delphine Bourneau-Martin[1], Marie Briet[1,11,12]

[1]Department of Pharmacology-Toxicology and Pharmacovigilance, University Hospital of Angers, Angers, France. [2]CRPV CHRU NANCY-BRABOIS, VANDOEUVRE LES NANCY, France. [3]Department of Medical and Clinical Pharmacology, Regional Pharmacovigilance Center of Toulouse, Clinical Investigation Center 1436, Toulouse University Hospital, Toulouse, France. [4]Université de Bordeaux, Department of Medical Pharmacology, Bordeaux-DROM Regional Center of Pharmacovigilance, Bordeaux, France. [5]Department of Clinical Pharmacology & Pharmacosurveillance-Pharmacovigilance Center, University Hospital of Marseille, Marseille, France. [6]Centre régional de pharmacovigilance de Strasbourg Hôpital Civil de Strasbourd, Strasbourg, France. [7]Centre regional de PHarmacovigilance Nord Pas de Calais- CHU Lille, Lille, France. [8]Department of Clinical Pharmacology - Pharmacovigilance Center, University Hospital of Amiens-Picardie, Amiens, France. [9]Centre régional de pharmacovigilance de Rouen CHU de Rouen, Rouen, France. [10]Centre Régional de Pharmacovigilance et d'information sur le Médicament de Franche-Comté, CHU de Besançon, Besançon, France. [11]Université d'Angers, Angers, France. [12]Laboratoire MitoVasc, UMR CNRS 6214 INSERM 1083, Angers, France

Introduction: The mass COVID-19 vaccination campaign was accompanied by a reinforced surveillance and an unprecedented increase in adverse event reporting to pharmacovigilance centers. Cases of capsulitis have been reported since the beginning of the vaccination campain.
Aim/Objective: To analyze cases of shoulder capsulitis occurring after COVID-19 vaccination using data from the French National Pharmacovigilance Database (FPVD) and to investigate this risk in VigiBase®, the WHO pharmacovigilance Database.
Methods: Methods. A retrospective study of capsulitis cases reported between January 1, 2021, and August 19, 2022, was conducted using the FPVD using the following keywords: "capsulitis," "adhesive capsulitis", "shoulder capsulitis," "exacerbated shoulder freezing," and "frozen shoulder" and then those including the word "capsulitis" in the comments. Cases were reviewed by pharmacovigilance experts to select only capsulitis cases. A case/non case study was performed using cases reported in VigiBase® until March

19th, 2023. The disproportionality of capsulitis event related to COVID-19 vaccine was computed using the Reporting Odds Ratio (ROR). The control group consisted of cases where injectable vaccines other than covid-19 were single suspected.

Results: Two hundred and five cases of capsulitis were included, mean age 53 years (range 26-79), and female accounted for 77.6% of cases. The median time to onset of capsulitis was 48 hours after vaccination. mRNA vaccines were the most commonly administrated, 41.5% and 39.5% of cases occurred after the first and second vaccination doses respectively. At the time of reporting, 73% of patients had not recovered, with the mean time from vaccination to reporting being 5.2 months. Intracapsular injections were described for 9 patients. Three cases of positive rechallenge have been notified. Reporting was equally distributed between patients (57.2%) and healthcare professionals (47.3%). Signal of disproportionate reporting was found for capsulitis and COVID-19 vaccines (ROR = 1.99, 95% Confidence Interval = 1.7, 2.33).

Conclusion: This descriptive study reports a large number of cases of shoulder capsulitis occurring after COVID-19 vaccination. These findings represent a potential signal for pharmacovigilance. A suboptimal injection technique leading to an acute and prolonged hyperinflammatory local reaction is one hypothesis put forward(1). However, a causal link cannot be formally established. Since shoulder pain is a frequent reason for primary care consultation, awareness of this condition in a post-vaccination context could enhance patient management strategies.

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Artificial Intelligence: Revolutionizing Pharmacovigilance for Enhanced Drug Safety

Khadija LECHHEB[1], Achraf RACHID[1], Yassir BOUSLIMAN[1,2]

[1]MOHAMED V MILITARY HOSPITAL, RABAT, Morocco. [2]Faculty of medecine and pharmacy, RABAT, Morocco

Introduction: The healthcare and pharmaceutical landscape's evolution demands vigilant drug safety monitoring. Pharmacovigilance, crucial for identifying, assessing, and mitigating post-market adverse drug reactions (ADRs), faces challenges in timeliness and depth of data analysis. Conventional methods struggle with proactive risk detection. The integration of artificial intelligence (AI)—with its capabilities in machine learning (ML) and natural language processing (NLP)—into healthcare offers transformative potential, enhancing patient safety outcomes and care quality [1]. AI's adeptness at navigating vast data and uncertainty positions it as a natural fit for pharmacovigilance tasks [2], revolutionizing drug safety monitoring.

Aim/Objective: This study aims to investigate the potential of Artificial Intelligence (AI) in overcoming the limitations inherent in traditional pharmacovigilance practices, particularly focusing on enhancing timeliness, the breadth of data analysis, and proactive risk detection.

Methods: We conducted a systematic review to identify studies examining the role of AI in pharmacovigilance. Searches were performed in databases such as PubMed, Embase, and Web of Science up to December 2023, using keywords such as "AI in pharmacovigilance," "machine learning in drug safety," and "natural language processing in ADR detection." The selection criteria were aimed at articles demonstrating AI's impact on adverse event detection, signal analysis, and the creation of predictive risk models.

Results: Twenty-seven articles were selected for evaluation. The breakdown of the topics covered in these articles showed a significant focus on the use of machine learning for detecting adverse drug events (ADEs) and adverse drug reactions (ADRs), accounting for 55.55% of the articles. Natural language processing for drug safety was the focus of 25.92% of the articles, followed by the extraction of drug–drug interactions (14.81%), and the prediction of side effects (3.70%).

Conclusion: AI holds immense potential to transform pharmacovigilance into a more proactive, data-driven, and patient-centered practice. By overcoming the challenges and fostering a collaborative environment, AI can significantly contribute to safeguarding public health through enhanced drug safety monitoring. As we navigate this new frontier, the focus must remain on harnessing the power of AI to optimize patient outcomes and ensure the safe use of medications

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Acute Hepatitis and Phytovigilance: A Case Report

Fatima AIT EL HADJ[1,2], Afaf Bpouqoufi[2], youssef KHABBAL[2,1]

[1]Departement of pharmacology, University hospital SOUSS MASSA, AGADIR, Morocco. [2]Laboratory of Resaerch and Innovation in Health Science LARISS, Faculty of Medecine and Pharmacy, Ibn Zohr University, AGADIR, Morocco

Introduction: The metabolic function of the liver and its relationship with the gastrointestinal tract make it an important target for drug and xenobiotic toxicity. The hepatic metabolism of xenobiotics, often characterized by an imbalance between the production of toxic metabolites and detoxification processes, can influence the degree of hepatotoxicity [1].

Hepatotoxicity induced by drugs or environmental xenobiotics should be considered in cases of identified exposure, or when other causes of liver disease have been ruled out. Treatment is often non-specific; the most important intervention is rapid discontinuation of the drug or elimination of the environmental toxin[1]

Aim/Objective: case report

Methods: We report a cese of severe acute hepatitis occurring 15 days after ingestion of a preparation based on *Anis*, *Sesame*, *Garance (Rubia)*, and *Badiane* in a 33-year-old patient with no previous pathological history.

Results: Although a large body of research has demonstrated that *Rubia cordifolia* possesses numerous pharmacological activities with excellent therapeutic effects and low clinical side-effects, some compounds isolated from this plant remain toxic. The toxicity of crude ethanol extracts from R. cordifolia fruit was assessed by biochemical parameters and histopathological changes, and revealed harmful effects on the liver[2].

Conclusion: The Consumption of medicinal plants without knowledge of their toxicity profile can have unexpected effects on kidney and liver function, therefore assessing the toxicity of medicinal plants is important for understanding their safety profile.

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ISoP Medication Errors SIG: Integrated Antimicrobial Resistance Action (IARA) Program

Hager Saleh[1,2], Brian Edwards[3,2]

[1]Department of Global Public Health, Health Systems and Policy, Karolinska Institutet, Stockholm, Sweden. [2]International Society of Pharmacovigilance (ISoP), Medication errors Special Interest Group, London, United Kingdom. [3]Managing Director Husoteria ltd, Pharmacovigilance & Drug Safety, London, United Kingdom

Introduction: The Integrated Antimicrobial Resistance Action (IARA) Program presents a comprehensive strategy to combat antimicrobial resistance (AMR) through the integration of education, training, collaboration, data analysis, and advocacy efforts, the IARA Program emphasizes a holistic approach to address the challenges posed by AMR. This plan, incorporating feedback from experts, underscores the pivotal role of pharmacovigilance in identifying AMR, tackling behavioral challenges in antibiotic prescribing, and promoting reporting of inappropriate antibiotic use.
Aim/Objective: The Integrated Antimicrobial Resistance Action (IARA) Program aims to combat antimicrobial resistance (AMR) by raising awareness, providing education, fostering collaboration, strengthening pharmacovigilance efforts, and advocating for responsible antibiotic use. Key objectives include developing resources, conducting training, initiating collaborations, collecting data on medication errors and resistance patterns, and launching advocacy campaigns during AMR week. Through these actions, the IARA Program seeks to address the critical challenges posed by AMR and promote effective antibiotic stewardship.
Methods: The action plan outlines specific activities to be undertaken in each quarter over a two-year period. we will develop a subgroup within ISoP specifically focused on AMR initiatives and liaise with eco-pharmacovigilance and risk communication SIGs. Activities include finalizing the plan, launching educational webinar series, identifying knowledge gaps, developing guidelines, conducting research, planning and executing advocacy campaigns, and evaluating progress. Collaboration with organizations such as the World Health Organization, Centers for Disease Control and Prevention, pharmaceutical companies, and non-governmental organizations is essential for a comprehensive approach to addressing AMR. Social media strategies and integration into ISoP's annual meeting further enhance the program's reach and impact.
Results: Examples of the activities of the SIG will be shared.
Conclusion: By implementing these actions and fostering collaborations with key stakeholders, the ISoP Medication Errors SIG can contribute significantly to achieving the goals of the Integrated Antimicrobial Resistance Action Program and combating antimicrobial resistance effectively.
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Are Men and Women Equal When it Comes to Valproates—Analysis of Prescribing practice in Montenegro

Veselinka Vukicevic[1,2], Snezana Mugosa[1,2], Sandra Vezmar Kovacevic[3]

[1]Institute for Medicines and Medical Devices (CInMED), Podgorica, Montenegro. [2]Faculty of Medicine, University of Montenegro, Podgorica, Montenegro. [3]Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia

Introduction: In Montenegro, valproates (valproic acid, sodium valproate) are approved for the treatment of epilepsy and bipolar disorder. As in the EU countries, Pregnancy Prevention Programme (PPP) was implemented in December 2018 [1]. In February 2024, new measures were introduced, due to potential risk of neurodevelopmental disorders in offspring related to paternal exposure to valproates [2].
Aim/Objective: To analyse gender differences in prescribing of valproates in Montenegro; to assess the impact of the PPP.
Methods: An observational, retrospective, nationwide study was performed. Primary care information system was used as data source. The consent of the public Health Insurance Fund was obtained. We analysed anonymised prescription data on the country level, in the period 2016 - 2022, stratified by year, gender, indication and age group. Consumption data collected by CInMED was also analysed. Descriptive statistics was used.
Results: Consumption of valproates in Montenegro increased from 0.64 ddd/1000 inhabitants/day in 2016 to 0.87 ddd/1000 inhabitants/day in 2022. Number of patients who received at least one prescription for valproates increased from 3583 in 2016 (prevalence rate 0.6%) to 4477 in 2022 (prevalence rate 0.7%) while the number of dispensed prescriptions increased from 26 298 to 33 135, respectively. The majority of patients were men during the whole period (56.1% in 2016, 59.8% in 2022). Patients of reproductive age (12-55 years old) participated with 65.5% of all patients in 2016 and 60.7% in 2022. Share of women of reproductive age (12-55 years) in overall prescribing of valproates showed a decline after the implementation of the PPP from 24.8% in 2018, to 21.7% in 2022. The percentage of women age 12-20 in overall prescribing of valproates also showed a similar decline from 2.8% in 2018 to 1.7% in 2022. Moreover, the average number of dispensed prescriptions to women of reproductive age decreased with some fluctuation, from 7.5 in 2018, to 7.2 in 2022.

Table 1: Number of patients of reproductive age who received at least one valproates prescription

Year	Female patients		Male patients	
	12-55 years old	12-20 years old	12-55 years old	12-20 years old
2016	966	122	1382	205
2017	981	121	1381	205
2018	928	104	1430	207
2019	975	102	1483	214
2020	900	87	1473	194
2021	940	93	1599	195
2022	974	77	1744	209

Conclusion: Although overall consumption of valproates increased, prescribing of valproates to women of reproductive age in Montenegro decreased after PPP implementation. Detailed analysis of the patients' data will be performed to assess the impact of the PPPP in Montenegro, comparing to EU countries [3–5]. Prescribing of valproates to male patients of reproductive age should be monitored due to new safety concerns. Information system of primary care is a valuable data source for Pharmacovigilance research in Montenegro.
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Questionnaire-Based Survey Investigating ADR Spontaneous Reporting Knowledge, Experiences and Attitudes in Italian Oncology Wards

Marco Bonaso[1], Elena Berti[2], Concetta Calabrò[3], Sabrina Orzetti[4], Paolo Baldo[5], Marco Tuccori[1,6]

[1]Unit of Pharmacology and Pharmacovigilance, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy. [2]Pharmacy Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy. [3]S.C. Farmacia and U.Ma.C.A, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy. [4]Pharmacovigilance Clinical Desk, Centro di Riferimento Oncologico di Aviano - CRO Aviano, IRCCS, Aviano, Italy. [5]Hospital Pharmacy Unit, Centro di Riferimento Oncologico di Aviano - CRO Aviano, IRCCS, Aviano, Aviano, Italy. [6]Unit of Adverse Drug Reaction Monitoring–University Hospital of Pisa, Pisa, Italy

Introduction: Underreporting is a major problem of spontaneous reporting of adverse drug reactions (ADRs) in pharmacovigilance. This problem is particularly relevant in oncology for many reasons that are peculiar to healthcare workers (HCWs) in this field, such as for instance a different sensitivity towards ADRs, probably related to the habit of the high toxicity of the treatments used. [1, 2]
Aim/Objective: To describe the factors that limit ADRs reporting from the perspective of HCWs in the Italian oncology clinical setting.
Methods: This study was an initiative of the ISoP Italian Chapter. A quantitative descriptive study was conducted using an anonymous questionnaire aimed at assessing the sociodemographic characteristics of the participants, their knowledge of pharmacovigilance and their attitude to report ADRs (October 2023–February 2024). The questionnaire was assembled by adapting and integrating openly available published questionnaires with the support of experts in the assessment of ADRs in oncology settings and organized in 3 sections (demographic, knowledge, and attitude & experience). The questionnaire was accessible online on the surveymonkey.com platform and disseminated to target HCWs with the support of Italian Regional Pharmacovigilance Centres.
Results: A total of 388 HCWs participated in the survey. The completion rate of the questionnaire was 95% (N = 369 answers) for the demographic data section, 91% (N = 354 answers) for knowledge section and 69% (N = 269 answers) for the attitude & experience section. The most common age range was 30 to 49 years (N = 205/369; 56%), and 74% (N = 272/369) of participants were women. Most participants were physicians (N = 143/369; 39%), followed by nurses (N = 112/369; 30%) and pharmacists (N = 84/369; 23%). Approximately 46% (N = 124/269) of participants had not reported an ADR in the last year and of these 21% (N = 26/124) did not yet know the reporting system. In general, physicians and pharmacists were more knowledgeable about the reporting system than nurses. The main barriers to reporting were considered to be lack of time to report ADRs (N = 142/269; 53%), uncertainty about the causality of the reaction (N = 72/269; 27%), and difficulty in completing the reporting form (57/269; 21%).
Conclusion: These results suggest the need for targeted interventions to raise awareness and support HCWs in the reporting process, in order to ensure more complete and accurate data collection on the safety of cancer therapies.

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Cyclin-Kinase 4/6 Inhibitors and Renal Failure: a Study Based on the French National Pharmacovigilance Database

Kiara Coulombe[1], Anais Gaiffe[2], Romane Freppel[3], Aude Lambert[4], Jean-Luc Cracowski[5], Laurence Lagarce[1], Marie Briet[1]

[1]Centre Hospitalo-Universitaire d'Angers, Angers, France. [2]Centre Hospitalo-Universitaire de Besançon, Besançon, France. [3]Centre Hospitalo-Universitaire de Dijon, Dijon, France. [4]Hôpitaux Universitaire de Strasbourg, Strasbourg, France. [5]Université Grenoble Alpes, Grenoble, France

Introduction: Cyclin-kinase (CDK) 4/6 inhibitors–palbociclib, abemaciclib, and ribociclib - belong to a new pharmacological class of antitumoral agents indicated in locally advanced or metastatic breast cancer. Preclinical studies have shown an inhibitory effect of these agents on OCT-2 (Organic cation transporter 2) and MATE (Multidrug and toxin extrusion), which are involved in creatinine secretion. However, case reports suggest that these agents may also cause direct or indirect renal injury.
Aim/Objective: To evaluate renal adverse effects of CDK inhibitors based on reported cases in the French national pharmacovigilance.
Methods: Cases were extracted from the French Pharmacovigilance database using the terms SOC "renal and urinary disorders » and HLT "renal function analyses" with palbociclib, abemaciclib, or ribociclib as the suspected or interactive drugs from 2016 to January 9th, 2024. Each case was reviewed by a pharmacovigilance expert to select the cases related to renal injury and involving a CDK inhibitor.
Results: Forty-seven cases were included involving palbociclib (n = 16), ribociclib (n = 9), and abemaciclib (n = 22). In 2 cases, a pseudo-renal insufficiency was diagnosed, involving abemaciclib and palbociclib with complete resolution upon cessation of the medication. In 17 cases, pre-renal renal failure in the context of dehydration, mostly

related to diarrhea or vomiting (n = 14/17), was reported, mainly involving abemaciclib (n = 14/17). The median of peak of creatinine was 242 µmol/L (min 95-max 988µmol/L). Rechallenges were negative in 2 cases and positive in 3 cases. Evolution was favorable in 16 cases. Finally, renal injury without dehydration context was diagnosed in 28 cases involving palbociclib (n = 14), ribociclib (n = 7) and abemaciclib (n = 7). CDK inhibitor was stopped in 23 cases and maintained in 2 cases. The median peak of creatinine was 195µmol/L (min 138-max 548µmol/L). A renal biopsy was performed in 2 cases showing tubular necrosis lesions in the first case and tubulointerstitial nephritis in the context of IgG4 disease in the second case. The evolution was favorable (completely or ongoing) in 21 cases, resolved with sequelae in 1 case, non-resolved in 5 cases. A positive rechallenge was observed in 3 cases and no negative rechallenge was reported.

Conclusion: In addition to the pseudo-renal insufficiency well-described with CDK inhibitors, this study underlines a renal toxicity in the context of CDK inhibitor exposure with a favorable evolution when the drug was stopped in the majority of the cases. The clinic/biological presentation suggests NTA lesions, histologically confirmed in one case. This study suggests that attention should be paid to renal function in the exposed population.

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Major Adverse Cardiovascular Events Related to Jak Inhibitors: A Disproportionality Analysis Using WHO Global Individual Case Safety Database

Raffaella Di Napoli[1,2], Christophe Richez[3], Cristina Scavone[1], Allison Singier[2], Maxime Demorgues[4], Annamaria Mascolo[1], Annalisa Capuano[1], Francesco Salvo[2,4]

[1]Department of Experimental Medicine–Section of Pharmacology "L. Donatelli", University of Campania "Luigi Vanvitelli", Napoli, Italy. [2]Université de Bordeaux, INSERM, Bordeaux Population Health, U1219, Bordeaux, France. [3]Service de Rhumatologie, Centre de référence des maladies auto-immunes systémiques rares RESO, Hôpital Pellegrin, Centre Hospitalier Universitaire, Bordeaux, France. [4]CHU de Bordeaux, Service de Pharmacologie Médicale, Centre Régional de Pharmacovigilance Bordeaux-DROM, Bordeaux, France

Introduction: Rheumatoid arthritis (RA) is a polygenic, multifactorial and chronic immune-mediated disease [1]. Recently, in Europe, the Pharmacovigilance Risk Assessment Committee (PRAC) suggested avoiding the use of JAK inhibitors (JAKis) as a first-line alternative to methotrexate in patients with cardiovascular (CV) risk factors, such as age ≥65 years [2]. Despite established recommendations, there is currently limited evidence on MACE in elderly and adult patients in real-world settings, and there is also a lack of studies analysing individual MACE events, such as stroke or myocardial infarction, and providing information on their risk function (e.g. time to onset after drug initiation).

Aim/Objective: This study aimed to describe the individual case safety reports of major adverse cardiac events (MACE) or stroke and determine if there was a difference in the probability of reporting cardiovascular events between JAKis and anti-TNFα used in RA.

Methods: A case/non-case study was carried out using reports collected in the WHO database, VigiBase®. A descriptive analysis was performed, the time-to-onset between JAKis start and MACE was calculated (median and interquartile range, IQR), and the reporting odds ratio (ROR) was used to estimate the likelihood of reporting outcome of interest with JAKis compared to anti-TNFα used in rheumatoid arthritis.

Results: A total of 17,187 cases of MACE were retrieved, 2,037 of which (11.8%) exposed to JAKis, mostly in women (64.8%) and in patients of ≥ 65 years (52.3%). Median time-to-onset was 240 days [IQR 60 to 570] for JAKis, and 730 days [300 to 1,825] for anti-TNFα. JAKis were associated with a higher odds of reporting MACE (ROR 1.22 [95% CI 1.17 to 1.28]), due in particular to non-fatal stroke (1.43 [1.33 to 1.52]). Stroke as a whole showed similar results (1.40 [1.32 to 1.50]). Likelihood of MACE was slightly increased also in patients with < 65 years treated with JAKis (1.15 [1.17 to 1.24]).

Conclusion: Compared to anti-TNFα, JAKis were more related to MACE, in particular to stroke, and with a shorter time-to-onset. These data support the hypothesis of a different CV risk profile between JAKis and anti-TNFα. In patients with identified cardiovascular risk, preference should be given to anti-TNFα over JAKis, pending more definitive results.

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Impact of Additional Risk Minimization Measures on Prescribing Patterns: An Interrupted Time Series Analysis

Szandra Marton[1], Eszter Puhl[1], Mátyás Pétervári[1,2], Zsolt Varga[3], Péter Ferdinandy[1,4], Bence Ágg[1,4]

[1]HUN-REN–SU System Pharmacology Research Group, Department of Pharmacology and Pharmacotherapy, Budapest, Hungary. [2]Sanovigado Ltd, Budapest, Hungary. [3]Centre of Science & Innovations Vice-Rector and Business Development, Semmelweis University, Budapest, Hungary. [4]Pharmahungary Group, Szeged, Hungary

Introduction: Implementing routine and additional risk minimization measures (aRMM) can play a crucial role in preventing adverse drug reactions (ADR). While these measures hold promise for improving patient safety, current methods for assessing their effectiveness often focus on coverage or awareness, rather than measuring clinically relevant outcomes [1-4]. The inconsistent methodologies and evaluation criteria across these studies underline the need for a standardized, straightforward approach.

Aim/Objective: This study aims to assess the effectiveness of aRMMs for tolperisone using drug dispensation data.

Methods: We analyzed the monthly dispensation of our target medicine in Hungary and Czechia using interrupted time series (ITS) analysis. By comparing pre- and post-implementation trends, this approach can describe the impact of an intervention. Reported adverse reactions considered as safety concerns were examined using the EudraVigilance database.

Results: In our analysis of Hungarian tolperisone dispensation data, we found the first intervention did not prove effective (p = 0.146). However, the second aRMM had a significant impact (p = 0.026). The results for the Czech aRMM for did not show statistical significance (p = 0.347).

Conclusion: We demonstrated the application of ITS to evaluate the effectiveness of aRMMs utilizing drug dispensation data, providing valuable insights into their real-world influence on clinical practice.

The successful implementation of this method holds promise for enhancing safe use of medications.

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Effectiveness of Educational Materials as Additional Risk Minimization Measures for Faricimab (Vabysmo®), Aflibercept (Eylea®) and Ranibizumab (Lucentis®)—The MARVEL Study

Inês Tavares[1,2], Joana Rita Abrantes[1,2], João Paulo Fernandes[3], Márcia Silva[3], Lisete Lemos[1,2,4]

[1]Pharmacovigilance Unit of Coimbra, AIBILI–Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal. [2]DruSER.Net–Drug Safety and Effectiveness Research Network, Coimbra, Portugal. [3]INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon, Portugal. [4]Coimbra Hospital and University Centre (CHUC), Coimbra, Portugal

Introduction: Antineovascularization agents are used to treat highly prevalent diseases such as age-related macular degeneration, diabetic macular oedema and retinal vein occlusion [1]. Educational materials (EM), as additional risk minimisation measures, are implemented in Portugal by the marketing authorisation holders with the previous agreement of the Portuguese National Competent Authority (INFARMED, I.P.). The EM implemented for antineovascularization agents subject to this study [2] aim to address and manage the important identified risks of endophthalmitis, intraocular inflammation, intraocular pressure increase, retinal detachment and tear and traumatic cataract.

Aim/Objective: The MARVEL study aims to assess the effectiveness of EM, targeted for Healthcare Professionals (HCP) and patients, for three medicinal products: faricimab (Vabysmo®), aflibercept (Eylea®) and ranibizumab (Lucentis®). The primary objective is to assess the reception and viewing of these EM by HCP and patients. The secondary objective is to assess the understanding of key safety messages and adherence to conscientious behaviour consistent with these messages.

Methods: This non-interventional post-authorisation safety study, registered in ENCePP (EUPAS106809), was conducted using two anonymous online questionnaires, one for ophthalmologists who prescribed at least one of the three medicinal products under study in the previous year and another for patients who received treatment with at least one of the three medicinal products under study in the previous year, in Portugal. The data were collected from September until December 2023 and were analysed with descriptive statistics.

Results: Thirty-one valid questionnaires were collected for the HCP population, and 114 valid questionnaires were collected for the patient population. Of the faricimab (Vabysmo®)-prescribers (N = 12), 75% had access to the EM, and 8% distributed and discussed its contents with the patients. Of the aflibercept (Eylea®)-prescribers (N = 31), 48% had access to the EM and 6% distributed and discussed its contents with patients. Of the ranibizumab (Lucentis®)-prescribers (N = 20), 50% had access to the EM and 5% distributed and discussed its contents with patients. Of the 114 patients, only 2% reported having received any EM, either through HCPs delivering these materials or through autonomous research.

Conclusion: The study provides valuable insights into measuring the effectiveness of EM as risk minimisation measures. Results show that about half of the surveyed HCPs have access to EM, but very few discuss them with patients. For patients, only a small number have access to EM. Further analysis is being conducted regarding the level of knowledge of key safety messages in both populations.

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Pulmonary Embolism and COVID-19 Vaccinations in 2021 and 2022: A Study in a Swedish Population of 7.5 Million People

Anders Sundström[1,2], Sofia Attelind[1,2], Björn Zethelius[1], Rickard Ljung[1]

[1]Swedish Medical Products Agency, Uppsala, Sweden. [2]Uppsala University, Uppsala, Sweden

Introduction: During the COVID-19 vaccination campaign in Sweden in 2021 and 2022, pulmonary embolism (PE) was one of the most reported suspected serious ADR to the Swedish Medical Products Agency.

Aim/Objective: To estimate the risk of PE following vaccination for COVID-19 in the entire Swedish population aged 18 to 84 years.

Methods: Within the CoVacSafe-SE register study[1], we identified incident cases of PE in the Swedish Patient Register[2] occurring between 27-Dec-2020 and 31-Dec-2022. Date and type of administered COVID-19 vaccine and positive COVID-19 tests were obtained from registers at the Public Health Agency of Sweden. Information on prescribed drugs was obtained from the Swedish Prescribed Drug Register and socio-demographic information from Statistics Sweden. A period of 28 days after each vaccine dose was considered time at risk. The vaccines are identified as BNT (Comirnaty®), MOD (Spikevax®) and AZ (Vaxzevria®) without regard to variants. A multi-variable Cox proportional hazards' model was fitted where individuals were followed up until first diagnosis of PE, a positive COVID-19 test, the sixth COVID-19 vaccination dose, emigration, death or end of follow-up. The Swedish Ethical Review Authority approved the study (2020-06859 and 2021-02186).

Results: Eighty percent of the study-population ($\approx$6.1 million people) received at least two doses of COVID-19 vaccine. A total of 13,357 cases of PE were identified, of which 1,861 (13.9%) within the defined risk-window. Crude and adjusted (for i.a. age, sex, co-morbidities) Hazard Ratios (HR) for the 10 most common vaccinations (94% of all cases) are listed in Table 1.

Table 1. Vaccine dose number and type, number of vaccinees, number of cases of Pulmonary Embolism, adjusted Hazard Ratios for the ten vaccination schemes with the highest number of vaccinees.

Dose # - Vaccination	Vaccinees	Cases	HR adj
1 BNT	4,728,309	391	1.17 (1.04-1.30)
2 BNT (after 1 BNT)	4,596,244	331	1.05 (0.93-1.18)
3 BNT	3,172,145	325	1.15 (1.00-1.31)
4 BNT	1,678,378	174	0.97 (0.82-1.14)
3 MOD	1,325,352	108	1.11 (0.91-1.36)
5 BNT	1,015,700	142	0.93 (0.77-1.12)
1 MOD	804,503	51	1.05 (0.79-1.39)
2 MOD (after 1 MOD)	732,312	45	1.01 (0.75-1.36)
1 AZ	706,211	107	1.26 (1.03-1.54)
2 AZ (after 1 AZ)	569,303	70	0.99 (0.77-1.26)

The highest number of PEs, 391, was observed after the 1st dose of BNT, yielding an HR_{adj} of 1.17 (95% CI 1.04-1.30), whilst the highest HR_{adj}, 1.26 (95% CI 1.03-1.54), was seen after dose 1 of AZ.

Conclusion: In this nation-wide study of more than 13,000 cases of pulmonary embolism, no strong associations were found with COVID-19 vaccinations. The small increases in risk for the early doses of vaccines may be associated with prioritizing the most frailty groups of people in the national vaccination campaign, thus selection bias or residual confounding may not be ruled out.

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Awareness of Adverse Drug Reaction Reporting Among the Physicians in Georgia

Nino Silagadze, Nino Ganugrava, Marina Darakhvelidze, Elza Nikoleishvili

School of Health Sciences, University of Georgia, Tbilisi, Georgia

Introduction: Globally, the high prevalence of adverse drug reactions has increased morbidity and mortality rates in both the hospital and non-hospital sectors. Adverse Drug Reactions (ADRs) under-reporting remains a challenge to pharmacovigilance worldwide. Healthcare professionals (HCPs) play a key role in monitoring and reporting adverse drug reactions (ADRs). Pharmacovigilance system in Georgia is not effective and characterized with underreporting from health care professionals. [1-4]

Aim/Objective: To investigate awareness of adverse drug reaction reporting among physicians in Georgia.

Methods: We conducted a cross-sectional study to investigate awareness of adverse drug reaction reporting among physicians in Georgia. Data was collected by self-administered structured questionnaire from the physicians working in the medical institutions of Georgia from April 2023 to February 2024.

Results: Currently, 262 physicians responded to the questionnaire. 78.6% (n = 206) physicians stated that they had already observed an ADR in their working practice. However, only 17.2% doctors (n = 45) had ever reported one; of those, the different modes of reporting included the use of ADR report form in (3.4%) and the use of national ADR report by (1.9%). A verbal report to foreign pharmaceutical company's representatives, the managers of clinical centers, and sponsors of clinical studies (in case doctors were involved in clinical trilas) was reported by other cases.

When physicians ever suspected but did not report adverse drug reactions, 69.5% (n = 182)respondents cited the reasons for not reporting: 7.3% physicians (n = 19)were not sure that the reaction was caused by the drug; 21% doctors (n = 55) answered that they considered the adverse drug reaction to be too trivial to report; 68.3% physicians (n = 179) reported that they were unaware of the existence of a national adverse drug reaction reporting scheme; 51.9% (n = 136) respondents (responded that they were unaware of the need to report ADR and 60.68% physicians (n = 159) did not know how to report ADRs.

Conclusion: The result shows low adverse drug reaction reporting among the physicians and its association with low knowledge about the national adverse drug reaction reporting scheme. Based on the above, educational intervention is needed to train physicians to report adverse drug reactions.

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Knowledge Communities: What Are They, How Do They Work, and Why Are They Key to Strengthening the Global Pharmacovigilance Ecosystem?

Ryan Walker

The Global Health Network, Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, United Kingdom

Introduction: Collaborative networks aiming to facilitate knowledge exchange are ubiquitous in public health. Working groups, communities of practice, special interest groups, and coalitions abound, but the mechanisms by which these approaches contribute to lasting success are often poorly understood, even by those who lead and participate. It is imperative that the global pharmacovigilance community understands how such networks operate, where they overlap, and what value they offer to their members and scientific disciplines. Such understanding is essential for addressing the collective challenges facing pharmacovigilance stakeholders efficiently, and ensuring that the global pharmacovigilance workforce is upskilled in a sustainable and equitable manner.

Aim/Objective: To examine the impact of knowledge community approaches on the strengthening of the global pharmacovigilance ecosystem.

Methods: A global landscape analysis of existing knowledge communities with a focus on pharmacovigilance will be conducted, involving internet searches and consultation with pharmacovigilance experts. The analysis will collate publicly-available information on these initiatives and include exploration of; knowledge community type, goals, outputs, leadership/governance structures, geographical distribution, accessibility, funding sources, and monitoring and evaluating/impact assessment procedures. From this landscape analysis, key networks will be identified and explored in detail as case studies, to provide a comparative overview of contrasting knowledge community approaches to pharmacovigilance capacity strengthening, and discuss the impact of these approaches on the global pharmacovigilance ecosystem.

Results: Results will be presented in the form of a descriptive statistical analysis of the global network of pharmacovigilance knowledge communities, with particular focus on shared areas of

interest, goals, and mechanisms of operation and key gaps identified. In addition, a directory of the pharmacovigilance knowledge communities identified will be published open-access on globalpharmacovigilance.org.

Conclusion: It is anticipated that the findings from this study will inform recommendations to guide existing and future knowledge communities seeking to strengthen worldwide pharmacovigilance capacity, and contribute to increased collaboration, understanding, and equitable involvement in pharmacovigilance activities at a global scale.

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The American Program in Pharmacovigilance (Am2P): A New Accredited Training Program in Pharmacovigilance and Pharmacoepidemiology

Veronique Kugener[1], Karine Palin[2], Marina Malikova[3]

[1]*Takeda Pharmaceuticals, Cambridge, USA.* [2]*Université de Bordeaux, Collège Santé, Eu2P programme, Bordeaux, France.* [3]*Boston Medical Center, Boston, USA*

Introduction: Pharmacovigilance (PV) encompasses all scientific activities relating to the detection, assessment, and prevention of pharmaceutical products-induced adverse effects. In November 2021, the North American Society of Pharmacovigilance (NASoP), a Chapter of the International Society of Pharmacovigilance (ISoP) in collaboration with Eu2P institutions, launched an online PV program adapted to North America.

Aim/Objective: To review an online training resource available to PV trainees/professionals and to encourage PV professionals to continue their distance learning and education.

Methods: The Am2P program (Am2P) is an online North American focused program that follows the WHO-ISoP Core Elements of a Comprehensive Modular Curriculum and subscribes to the Innovative Medicines Initiative (IMI) Education and Training quality standards, which was jointly developed by Eu2P and other IMI Education and Training projects to foster quality in learning and professional development. Convenient online education in PV, the Am2P supports the mission of ISoP to foster PV scientifically, educationally and enhance the safe and proper use of medicines worldwide. Am2P was designed by PV experts within NASoP in partnership with Eu2P instructors with academic accreditation.

Results: Am2P offers two academic options: the Certificate degree and the Short Course certificate of achievement in PV. Four modular course programs provide education on core and specialized PV topics. Program approval is ensured by the Eu2P Executive Board including academic representatives of the six Eu2P degree-awarding universities.

Conclusion: Am2P, as a partnership between NASoP and Eu2P, offers accredited online PV training, focused on North America; to address the needs of new and experienced PV professionals.

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Applications of Artificial Intelligence and Machine Learning in Pharmacovigilance and Drug Safety

Karou Safaian[1,2], Grace Mosallam[3,2]

[1]*Takeda Pharmaceuticals - MCPHS University, Cambridge, MA, USA.* [2]*MCPHS University, Boston, MA, USA.* [3]*Biogen, Cambridge, MA, USA*

Introduction: Impact of artificial intelligence (AI) and machine learning (ML) on pharmacovigilance (PV) remains uncertain. AI is the science of designing systems exhibiting characteristics associated with intelligence in human behaviour'.[1]ML creates algorithms to accomplish a task while learning from successes and failures.[2,3] AI's and ML's potential in PV have been studied in improving safety operations, identification of target populations, and signal management.[2,3] AI integration into safety processes aims to improve patient safety, optimize drug development, and post-marketing surveillance. Thus, enhancing public health outcomes through improving case processing and identification & management of adverse drug reactions (ADR).4

Aim/Objective: The aim of this study is to provide a comprehensive understanding of the applications, motivations, and risks & challenges for integrating AI and ML into PV processes- specifically within, safety operations, identification of target populations, and signal management.

Methods: The PubMed and MedLine databases were searched to identify articles pertaining to the use of AI and ML in PV published within the last 5 years using the terms "pharmacovigilance", "artificial intelligence", and "machine learning". Article types were limited to systemic reviews, meta analyses, reviews, and books/documents. Article language was limited to English. Literature that included information on applications of AI/ML in safety operations, identifying target populations, and signal management in PV were reviewed and included.

Results: In safety operations, AI and ML could be useful in case processing, duplicate detection, anomaly identification, and assessment of reported causality in individual case safety reports (ICSRs).[4] Additionally, AI and ML can be implemented to identify patients at high risk of ADRs, predict drug side effects, and simulate clinical trials. Lastly, AI and ML has been used to identify safety signals through automated processes and training with ML models by detection and validation of signals.[4-6] Despite its benefits, implementation of AI and ML are associated with challenges including regulatory/legal concerns, algorithm biases, and integration into existing PV workflows and systems.[7-9]

Conclusion: Incorporation of AI and ML into safety operations, identification of target populations, and signal management is reshaping the landscape of drug development and presenting new opportunities to enhance patient safety outcomes. Although AI and ML are imperative for enhancing PV workflows and patient outcomes, its implementation must overcome the challenges and risks associated with its use.

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A Systematic Literature Review of the Long-Term Adverse Events Associated with COVID-19 Vaccines

Candice Drinkwater[1,2], Maribel Salas[3], James Januzzi[4], Anup Challa[5], Tarek Hammad[6], Armen Ghazarian[1], Maxine Gossell-Williams[7], Lubna Merchant[8], Rebecca Chandler[9], Rebecca Noss[10], Marina Malikova[11], Toluwalope Junaid[12]

[1]Daiichi Sankyo, Inc., Basking Ridge, USA. [2]Rutgers University, New Brunswick, USA. [3]Bayer AG, Whippany, USA. [4]Harvard University, Boston, USA. [5]AstraZeneca PLC, Gaithersburg, USA. [6]Takeda Pharmaceuticals Inc., Cambridge, USA. [7]The University of the West Indies, Kingston, Jamaica. [8]Pfizer Inc., Collegeville, USA. [9]Coalition of Epidemic Preparedness Innovations, London, United Kingdom. [10]Noss Research Consulting LLC, Columbus, USA. [11]Boston University, Boston, USA. [12]Syneos Health, Morrisville, USA

Introduction: Over 774 million confirmed cases of SARS-CoV-2 and over 7 million deaths have been reported as of March 2024. [1] The development of COVID-19 vaccines has demonstrated significant protection against severe disease and mortality, with around a 54% effectiveness rate against symptomatic SARS-CoV-2-infection. [2] The rapid development of COVID-19 vaccines and their unknown long-term safety profiles are important determinants in its acceptance. [3, 4] While acute adverse events have been studied, long-term adverse event studies remain scarce. Given this gap, we sought to summarize and evaluate the reported long-term adverse events associated with COVID-19 vaccines from the scientific literature.

Aim/Objective: To systematically summarize and describe the reported long-term adverse events of COVID-19 vaccines from the literature.

Methods: The search was conducted using Embase and Ovid MEDLINE databases restricted from January 2020 to September 2023 using the following terms: "long-term", "adverse events", "obstetrical", "gynecologic", "paralysis", "death", "cardiovascular", "neurologic", "endocrinologic", "pyrexia", "myalgia", combined with all globally available COVID-19 vaccines. The search was bound to studies published in English, adults ≥18 years vaccinated with COVID-19 vaccines, interventional and non-interventional studies, including peer-reviewed manuscripts, case reports, and scientific journals. Commentaries, editorials, opinions, and pediatric studies were excluded. This study was conducted following the PICO framework and PRISMA guidelines. Studies were first identified then proceeded by two levels of screening from different investigators. Two levels of data extraction were performed to ensure entitled research was selected. Descriptive statistics were used to summarize the results. Cochrane's Risk of Bias assessment toll was used to address bias and confounding of the included studies.

Results: A total of 3,729 articles were identified in the literature, and half of the articles were excluded during the first screening. From the remaining, we found that the long-term adverse events associated with COVID-19 vaccines vary depending on the type of COVID-19 vaccine. For example, cardiovascular events such as thrombosis, stroke, myocarditis, myocardial infarction, pulmonary embolism and arrhythmia were associated with mRNA vaccines with a lag time ranging between 4-6 days. The adenovirus-vector COVID-19 vaccines were associated with Guillian-Barre Syndrome, thrombosis and thrombocytopenia syndrome. The most frequent long-term adverse events included taste disturbances (bitter taste or metallic taste), fatigue, menstrual disturbances, myalgias, arthralgia, dizziness, and headache.

Conclusion: This study identified some potential long-term adverse events associated with COVID-19 vaccines. Long-term monitoring of adverse events will contribute to better characterize the safety profile of COVID-19 vaccines.

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Education in Pharmacovigilance, Creation of the Pharmacovigilance Classroom in Collaboration with the University of Granada

Jose Alberto Ayala Ortiz[1], Blanca Contreras Aguilar[1], Carmen García Alcaraz[1], Manuel Sanchez Polo[2], Miguel Romero Perez[2], Maria Jose Zarzuelo Romero[2]

[1]PVpharm, Almeria, Spain. [2]University of Granada, Granada, Spain

Introduction: There is an urgent need to organize coordinated activities between the University and the Industry for updating, perform professional training and support job placement of Health Sciences students, in the complex field of Pharmacovigilance and Drug Safety.

One of the specific aims of pharmacovigilance is to promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public(1).

Aim/Objective: The Pharmacovigilance Classroom in collaboration with the University of Granada is a space dedicated to increasing knowledge and learning about Pharmacovigilance and the Pharmaceutical Industry and it can be extrapolated to other Universities worldwide.

Methods: The interaction between the Industry and the University allows the acquisition of competencies and skills for students and graduates of the Health Sciences Degrees for their professional training and integration into the field of Pharmacovigilance.

Results: The creation of a space dedicated to increasing knowledge and learning about Pharmacovigilance and the Pharmaceutical Industry. The Classroom supports the implementation of training and dissemination activities in the field of Pharmacovigilance, a sector that has a direct influence on the safety of the medications consumed by patients.

Conclusion: This collaboration brings several areas of the pharmaceutical industry closer to the University, within a context of innovation in a global environment.

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Increase in Antibiotic Resistance in a Specialty Hospital Between Two Periods from January 2018 to December 2023: A Cross-Sectional Study

Jefferson Santiago Piedra Andrade[1,2], Carmita Leonor Medina Sucunuta[2], Juan Carlos Piedra Cosios[2], Luis Patricio Dávila Aguilar[2], Mónica Beatriz Castelo Loza[2], Gerardo David Salazar Loor[2], Fernando Xavier Torres Navas[2], Nicole Denisse Calvopiña Ramirez[2], Axel Damián Calvopiña Ramirez[2], Adonis Aarón Gavilanez Rodriguez[2], Leonel René Calvopiña Molina[2], Karina Judith Romero Contreras[2], Juan Alberto Narváez Olalla[3]

[1]Universidad de las Américas, Quito, Ecuador. [2]Hospital de Especialidades de las Fuerzas Armadas, Quito, Ecuador. [3]Universidad Central del Eduador, Quito, Ecuador

Introduction: Antimicrobial resistance has remained as a global concern. It´s increasingly exacerbated by the indiscriminate use of antibiotics. Pharmacovigilance related to the detection and communication of bacterial resistance is a fundamental axis in the management strategy.

Aim/Objective: The aim of this study was to compare the resistance of gram-negative and gram-positive organisms to the most common antibiotics in two time periods, January 2018 to December 2020 and January 2021 to December 2023, in the specialty hospital (third level) of the Armed Forces in Quito, Ecuador.

Methods: Data were collected from the microbiology service of the hospital. Diagnostic recommendations were used to request the microbiological study based on clinical practice guidelines depending on each infection. Samples of secretions from the nose, abscesses, nasopharynx, wounds, vaginal, tracheal, catheters, sputum, feces, bronchoalveolar lavage fluid, abdominal, pleural, cerebrospinal fluid, urine, blood and tissues with signs of infection were included. All cultures with bacterial growth sent to the laboratory from all clinical and surgical services of gram-negative and gram-positive bacteria were selected. In addition, interpretations of resistance to ceftriaxone, ciprofloxacin, erythromycin, gentamicin, tetracycline, and vancomycin were analyzed. The data was divided into two periods: from January 2018 to December 2020 and January 2021 to December 2023. The difference in the frequency of resistance of the two periods was analyzed.

Results: 8021 cultures with bacterial growth were analyzed. Significant changes in antibiotic resistance were evident between the periods 2018-2020 and 2021-2023. An increase in resistance to ceftriaxone in gram-negative organisms was evident from 37.85% to 62.15% ($p<0.01$). In gram-positive organisms, resistance to ciprofloxacin was 40.88% to 59.12%, and gentamicin from 25.84% to 68.90% ($p<0.01$). Furthermore, there was a significant increase in vancomycin resistance from 3.93% to 96.07% ($p<0.01$). No significant changes in resistance to ciprofloxacin and tetracycline were identified.

Conclusion: This study shows significant changes in antibiotic resistance between the periods January 2018 to December 2020 and January 2021 to December 2023 that coincided with the COVID-19 pandemic. These changes in antibiotic resistance may have important implications for the treatment of infections in the hospital that was studied. However, (followed research is required to undertand better these changes) more research is required to better understand these changes, especially those related to the pandemic.

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Update on the Initiatives Developed by the ISoP SiG on Risk Minimisation Methods

Jean-Christophe DELUMEAU[1,2], Hadir Rostrom[3,4]

[1]Institute of Pharmacovigilance, Prague, Czech Republic. [2]International Society of Pharmacovigilance, Geneva, Switzerland. [3]MSA University, Cairo, Egypt. [4]nternational Society of Pharmacovigilance, Geneva, Switzerland

Introduction: Initially focused on Asia, the SiG on Risk Minimisation Methods (the SiG) expanded its scope to other regions keeping a special attention to risk minimisation methods suitable for healthcare systems of developing economies, including innovations taking advantage from digital tools. Since ISoP 2023 (Bali), the customisable good vigilance practice project (GPvP) is under its scope. About 50 members from all regions are involved into this SiG organised according to 5 selected initiatives

Aim/Objective: The ultimate goal of the SiG is to ensure and speed-up globally the awareness of risk minimisation experience and innovation across all regions, and to improve the adequation of the methods to the diversity of specific health care systems, especially those of developing economies.

Methods: The developments conducted by the SiG are organised according to five initiatives: 1) the GPvP, 2) the Global RMP Annex, 3) the questionnaire for collecting experience and innovation in risk minimisation, 4) The online symposium on innovation in risk minimisation methods, 5) and setting-up standards for risk minimisation mobile applications. SiG members involved themselves on a voluntary basis depending on their availability. Considering the wide range of times zones covered, the working model is essentially the remote provision of input into documents, reserving teleconferences for strategic decisions on projects. The outcomes of those initiatives are intended to be published and made available in an open-source manner to the World Health Organization (WHO), National Regulatory Authorities and other stakeholders involved in public health.

Results: Initiative #1 (GPvP) consistent with a Maturity Level 3 (ML3) goal at the WHO Global Benchmarking Tool has reached an advanced stage. The development of a shorter version consistent with ML2 has started. Initiative #2 (Global RMP Annex) is also at an advanced stage. Initiative #3 (Risk minimization practice questionnaire) is underway, Initiative #4 (Symposium) is intended to be initiated in 2025, Initiative #5 was initiated earlier this year. Details and update will be provided in the presentation.

Conclusion: This presentation will elaborate on the strategy followed by the SiG to reach its public health goals via prioritised synergistic initiatives aimed to result into tangible open-source deliverables. Those initiatives are all developed in a voluntary manner with pro-bono resources kindly provided by the members of this SIG who should be recognised for their effective involvement. This paper will be presented on behalf of all active SiG members.

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Exploring Stakeholders' Experiences and Views on Capturing Traditional, Complementary, and Alternative Medicine Exposures in Routinely Collected Health Data

Aleksandra Milosavljevic[1], Mohammed Mohammed[1], Natalie Walker[2], Jo Barnes[1]

[1]School of Pharmacy, University of Auckland, Auckland, New Zealand. [2]School of Population Health, University of Auckland, Auckland, New Zealand

Introduction: At present, it is not known whether exposures to traditional, complementary, and alternative medicines and therapies ('TCAM') [1] are captured in routinely collected health data (RCHD) and whether RCHD have potential for examining associations between TCAM exposures and health outcomes. Patient-reported outcomes (PROs) - which reflect patients' views on their health [2] - may be important in this context, since many use TCAM for improving well-being and for other reasons that are not captured by clinical outcomes. As the prevalence of TCAM use is high globally, [3] users/potential users of RCHD may have views on capturing TCAM exposures in RCHD.

Aim/Objective: To explore stakeholders' experiences with, awareness of, and views on, the collection of i) patients' TCAM exposures and ii) PROs in RCHD.

Methods: This was a cross-sectional study using an online Qualtrics® questionnaire developed by the research team with expert panel input. Potential participants (RCHD researchers/users; RCHD managers/curators; TCAM researchers) were identified from: conference presentations and academic publications; two ISoP Special Interest Groups; authors of articles and curators of health datasets identified in a scoping review undertaken by the team. Potential participants were sent a personalised email invitation between January-March 2024. Ethics approval was granted by the Auckland Health Research Ethics Committee, New Zealand.

Results: Responses were received from 50/853 invited stakeholders (response rate: 5.9%). Table 1 presents a summary of participant characteristics. Most participants (n = 42, 84%) agreed/strongly agreed that most RCHD do not include patients' TCAM exposures and that this information should be included in RCHD (n = 45, 90%). Participants held differing views on the feasibility of capturing TCAM exposures in RCHD: 21 (42%) agreed/strongly agreed that currently it is not feasible to capture data on patients' TCAM exposures in RCHD, while 17 (34%) disagreed/strongly disagreed with this statement. Most participants (n = 42, 84%) would be interested in using patients' TCAM product exposures in their work if these were available in RCHD. Most participants (n = 41, 82%) agreed/strongly agreed that capturing PROs data together with patients' TCAM product exposures is important.

Table 1. Summary of characteristics of study participants (n=50)

		n (%)
Gender	Female	30 (60)
	Male	20 (40)
Age	≤ 30 years	1 (2)
	31-40 years	13 (26)
	41-50 years	15 (30)
	51-60 years	14 (28)
	≥ 60 years	7 (14)
Region of residence	Africa	3 (6)
	Asia	8 (16)
	Europe and UK	18 (36)
	Middle East	2 (4)
	North America	10 (20)
	Pacific	9 (18)
Participant category*	RCHD researchers/users	48 (96)
	RCHD managers/curators	21 (42)
	TCAM researchers	29 (58)

**Participant categories are not mutually exclusive*

Conclusion: These preliminary data come from a limited sample of RCHD researchers/curators and TCAM researchers. Participants recognised that information on TCAM exposures is rarely captured in RCHD, and there was some support among participants for taking steps towards including these exposures. Further work is needed to gain deeper insights into barriers and enablers towards routinely capturing such data. Also, these findings need to be examined among a larger sample, which is challenging given the low response rate.

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Sex Differences in Reporting Suspected Adverse Drug Reactions in Italy

Roberto Da Cas[1], Stefania Spila Alegiani[1], Cristina Morciano[1], Marco Massari[1], Alessandra Chillà[2], Roberta Ranalli[2], Maria Colamonico[2], Laura Sottosanti[2]

[1]National Centre for Drug Research and Evaluation, Italian National Institute of Health, Rome, Italy. [2]Italian Medicines Agency, Rome, Italy

Introduction: Biological differences by sex in responses to drugs and vaccines are well recognized and can stem from hormonal, enzymatic, and metabolic variations. Various studies based on pharmacovigilance data, have highlighted higher rates of adverse events in women compared to men [1]. These variations may be not limited to physiological factors, but may involve also social factors [2].

Aim/Objective: To describe the distribution of reports of suspected adverse drug reactions (ADR) in the Italian National Pharmacovigilance Network (RNF) in relation to sex.

Methods: Reports of ADRs to drugs registered in the RNF from 01/01/2022 to 30/06/2023 were analyzed, excluding reactions to vaccines and from literature. Analyses by age and sex were conducted by reporter's type, reaction's severity, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) classification of ADRs, and Anatomical Therapeutic Chemical (ATC) classification.

Results: During the study period, around 53,000 ADRs were analyzed with a rate per 100,000 inhabitants of 52.4 in males and 67.6 in females. Among children aged 2-11 years, there was a higher rate of reports for boys compared to girls. A higher rate of reports for females was observed across all other age groups, most significant disparity was noted in 18-44 years group. Additionally, fatal reports were higher among males. The highest difference between females and males were observed in ADRs reported by citizens. The SOC with a male dominance were "Neoplasms", "Endocrine disorders" and "Renal and urinary disorders". Rates higher than 65% were noted in females in "Pregnancy, puerperium and perinatal conditions", 'Ear and labyrinth disorders", "Musculoskeletal and connective tissue disorders" and "Reproductive system and breast disorders". Four ATC codes were more reported in males than females: urologicals, antithrombotic agents, anti-Parkinson drugs, and calcium channel blockers.

Conclusion: The analysis of ADRs to drugs in the Italian RNF pointed out differences between males and females in terms of reporter type, therapeutic category, and reported reactions. Sex disparities in ADRs are an important public health issue that requires

further investigations in order to ensure appropriate drug use and to improve the quality of healthcare.

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A Description of Environment-Related Reporting for Medicines in VigiBase

Joseph Mitchell[1,2], Robert Massouh[3,2], Ernest Dela Dzidzornu[4,2], Jayesh Pandit[5,2], Jerin Jose Cherian[6,7,2], Jose Maza Larrea[1]

[1]Uppsala Monitoring Centre, Uppsala, Sweden. [2]The ISoP Special Interest Group on Ecopharmacovigilance, ,, United Kingdom. [3]GSK, London, United Kingdom. [4]Independent Researcher, ,, Kenya. [5]Pharmacovigilance & Patient Safety Consultant, ,, Kenya. [6]Department of Global Public Health, Stockholm, Sweden. [7]Indian Council of Medical Research, New Delhi, India

Introduction: There is growing concern for the presence and inadvertent exposure to active pharmaceutical ingredients in the environment and there is an increased focus on environmental risks from medicines[1,2]. However, the focus of the environmental risks from medicines is often during the pre-authorisation phase of the product life[2]. There is not a standardised approach to the reporting or identification of suspected environment-related adverse events throughout the drugs lifecycle.

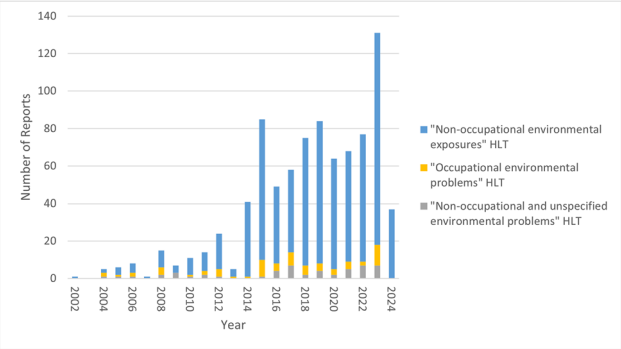
Aim/Objective: As part of work in the ISoP ecopharmacovigilance SIG, the aim was to describe the reported environment-related Preferred Terms in VigiBase, the WHO global database of adverse event reports for medicines and vaccines.

Methods: A search of VigiBase was performed on the dataset from March 20th 2024, the search terms for reported adverse events were the MedDRA Higher Level Terms (HLT) "Non-occupational and unspecified environmental problems", "Non-occupational environmental exposures", and "Occupational environmental problems". Vaccine-only reports were excluded and automatic de-duplication was performed[3]. A descriptive analysis was conducted of the most reported preferred terms (PT), reporter qualification, seriousness, and initial date of reporting. No case-by-case analysis and thus causality assessment was performed.

Results: In total, 866 reports were identified using 16 PTs and reports were received from 34 countries. The number of reports received, by year, for all HLTs is shown in Figure 1. The most frequent qualification of the reporter was "Consumer/Non-Health Professional" (n = 462, 53.3%), followed by "Physician" (n = 138, 15.9%). In total, 537 (62.0%) reports were marked as serious by the reporter.

A majority of the reports were for the HLT "Non-occupational environmental exposures" (n = 748, 86.4%), followed by "Occupational environmental problems" (n = 67, 7.7%), and "Non-occupational and unspecified environmental problems" (n = 51, 5.9%). The most reported PT in each HLT was "Heavy exposure to ultraviolet light" (n = 176), "Occupational problem environmental" (n = 40) and "Water pollution" (n = 32), respectively.

Figure 1. Number of Environment-Related Reports for Medicines Received by VigiBase by year and MedDRA Higher Level Group Term



Conclusion: VigiBase is a practical database for the reporting of suspected adverse events, including environmental exposure and the count of reports remains small, but is increasing. More awareness may stimulate more reporting, but reporting to VigiBase depends on a level of suspicion from the potential reporter which may not always be straightforward to establish. This initial review suggests the inclusion of some PTs of less relevance to environment-related exposure of medicines, and similarly there are terms related to inadvertent exposure in one's environment that may be of interest. Therefore, it may be beneficial to create a customised grouping of search terms to improve the relevance of the results.

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Multiple Evidences for Safety Evaluation of Chinese Patent Medicines

Jukai Huang[1], Guoqing Li[2], Tianyi Yang[3], Li Zhang[4], Bo Wang[5], Zhigang Zhao[6], Xiaohui Yang[1]

[1]Beijing university of Chinese medicine, Dongzhimen hospital, Beijing, China. [2]China Society for Drug Regulation, Beijing, China. [3]School of Environmental and Biological Science, Rutgers University, New Brunswick, NJ, USA. [4]Dongfang Hospital Affiliated to Beijing University of Chinese Medicine,, Beijing, China. [5]The Research Center of National Drug Policy & Ecosystem, Nanjing, China. [6]Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Introduction: Package Leaflets (PLs) are government-issued document that promote the safe and rational use of medicines. A few early-marketed Chinese Patent Medicines (CPMs) lack standardized pre-marketing clinical trial, post-authorisation efficacy study (PEAS) and post-authorisation efficacy study (PASS). The warning information of these CPMs PLs such as ADRs, contraindications and precautions are insufficient, which might lead to irrational drug use in clinical practice. The National Medical Products Administration (NMPA) has mandated Marketing Authorization Holders (MAHs) of related CPM to revise the PLs within deadline. Therefore, refining the safety information

of CPMs PLs with the current limited resource will significantly support MAHs in meeting NMPA's requirements, guiding the revision of PLs, relevant policies, and promoting rational drug use.
Aim/Objective: To develop a clinical safety information evaluation model of CPMs that reflects their intrinsic characteristics.
Methods: The Adverse Drug Reactions (ADRs) of CPMs were collected from spontaneous reporting systems (SRS), and the search of safety information of CPMs and prepared slices of Chinese crude drugs (PSCCDs) of the CPMs' formula based on the theory of traditional Chinese medicine (TCM), contraindications and precautions were recorded in "the Pharmacopoeia of the People's Republic of China" and "Instructions for Clinical Use of the Pharmacopoeia of the People's Republic of China". The search of contraindication of PSCCDs of the CPMs' formula was conducted in the databases of the Dictionary of TCM and the Chinese Materia Medica. Additional reviews, clinical studies, the Individual Case Safety Reports and therapeutic principle contraindications of CPMs were retrieved from databases such as CNKI, VIP, Wanfang, PubMed, the Science of Chinese Materia Medica, and the Pharmacology of TCM Formula and classical acient medical books. The collected safety information was evaluated by clinical and pharmaceutical experts, who then proposed signals and a multivariate evidence base for revision to these CMPs.
Results: Experts analyzed the safety information of the product and individual PSCCDs of the CPMs' formula based on the diversity of sources, the quality of information, and sample sizes, and subsequently identified the instinct and potential signals.
Conclusion: The revision of CPMs PLs faces great challenge due to the scarcity of source materials. The EWG Pharmacovigilance Research Committee of China Society for Drug Regulation(CSDR) has developed operational SOPs to provide technical guidance for MAHs to comply with NMPA regulatory requirements. To ensure the scientific and authoritative evidence for the revisions, MAH should actively enhance post-marketing pharmacovigilance and implement active surveillance, PAES and PASS for continuously evaluating the risk-benefit throughout the product life cycle. It is responsibility for the MAH ongoing monitoring the safety profile of approved products. Whenever new safety information is obtained from different sources, it should be evaluated to determine whether any revision to the CPMs information is needed.
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Strengthening Pharmacovigilance and Safety Surveillance in Bangladesh

Akter Farhana[1], Akter Hossain[2], Zahid SM Abu[1], vivian Rakuomi[3], Kate Kikule[4], Elizabeth woldemariam Teketel[5], Collins Jaguga[3], K Afsana[1]

[1]MTaPS, Dhaka, Bangladesh. [2]DGDA, Dhaka, Bangladesh. [3]MTaPS, Nairobi, Kenya. [4]MTaPS, VA Arlington, USA. [5]MTaPS, Addis Ababa, Ethiopia

Introduction: Pharmacovigilance (PV) is one of the key regulatory functions, which helps to ensure patient safety. Bangladesh Directorate General of Drug Administration/DGDA had its first WHO Global Benchmarking Tool (GBT) self-assessment in 2017.[1] PV function weaknesses identified included; insufficient adverse events (AE) reports; lack of policies, guidelines, regulatory framework. Poor capacity of healthcare facilities (HCFs) and healthcare providers (HCPs) , lack of PV system automation, poor periodic safety assessment by committees ,poor stakeholder engagement were obtained.
Aim/Objective: Strengthen PV in Bangladesh in accordance with the WHO GBT to improve patient safety and help the DGDA become a stable well-functioning regulatory authority
Methods: Based on GBT assessments done in 2017, 2018 and 2021 and the resulting institutional development plan, Medicines Technologies and Pharmaceutical Services Program/ MTaPS worked with DGDA to develop ,revise its regulatory framework and legal provisions in the National Drug Act; development of PV guidelines, processes, and procedures; PV Monitoring System (PViMS) implementation to automate AE spontaneous reporting, evaluation and integration with VigiFlow for data sharing; PV awareness training of HCPs to increase AE reporting; Expansion and institutionalization of PV to 30+ government and private HCFs, assessment of safety reports for decision making; establishment of COVID-19 vaccine safety surveillance system, capacity building of around1500 HCPs on Covid 19 system; provision of stakeholder feedback.
Results: The National Drug Act was approved in parliament and disseminated to 40 marketing authorization holders (MAHs). Pharmacovigilance issue has been incorporated with Clinical Trials and Lot Release in the newly approved the Drug and Cosmetics Act, 2023. Two PV guidelines and 15 procedures were developed or revised. PV was expanded institutionalized to more than 30 health facilities, with structures including PV focal person, and PV members with TOR. Approximately 950 HCPs have been trained in PV. As of April 3, 2024, 8 MAHs and 7 hospitals have submitted more than 250 AE reports through PViMS, 154 of them have undergone verification. DGDA has generated 50+ regulatory recommendations and acted, from 4500+ reports received through COVID 19 surveillance portal and 4000+ received manually on drugs and other vaccines. DGDA publishes periodic safety information through newsletters and websites. Integration of *need elaboration* (PViMS) data with Uppsala Monitoring Centre (UMC)'s VigiFlow is underway. In a 2024 GBT self-assessment, the PV **scored 99%** compared to 88% in 2021 and 67% in 2017.
Conclusion: The updated legal framework, improved AE reporting, regulatory recommendations and actions taken show MTaPS-supported PV interventions have helped DGDA, and health facilities to strengthen their PV capacity. PViMS is a very recently implemented system showing positive responds in Bangladesh. Automation of the AE reporting has increased reports and evaluation, and improved DGDA's efficiency and capacity to improve drug safety. However, more training on it and collaboration among stakeholders can definitely help in increased reporting, analyzing & sharing.
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A Self-Controlled Case Series Study to Evaluate Neurological Events After Influenza Vaccination In Italy: TheShinISS-Vax Flu Post-Marketing Surveillance

Cristina Morciano, Stefania Spila Alegiani, Maria Cutillo, Roberto Da Cas, Francesca Menniti Ippolito, Flavia Mayer, Ilaria Ippoliti, Arianna Annunziata, Giuseppe Marano, Marco Massari

National Centre for Drug Research and Evaluation, Istituto Superiore di Sanità, Rome, Italy

Introduction: The Italian National Institute of Health and the Italian Agency of Medicines coordinate the project TheShinISS-Vax|Flu, a post-marketing surveillance of influenza vaccines.

Aim/Objective: This Self-Controlled Case Series (SCCS) study aims to investigate the association of influenza vaccine with Guillain-Barré syndrome (GBS), Bell's palsy, encephalitis/encephalomyelitis during the 2021/2022 influenza vaccination campaign in Italy.
Methods: Study was based on linked data from health archives of Friuli Venezia Giulia, Emilia-Romagna, Lazio regions and a local health unit of Lombardia region, using the statistical tool TheShinISS. Study population was vaccinated and unvaccinated cases of GBS, Bell's palsy and encephalitis/encephalomyelitis aged ≥ 6 months, identified through emergency care/hospital admission using ICD9-CM codes. Observation period was 1st September 2021-30th June 2022. The SCCS method, adapted to event-dependent exposure, estimated Relative Incidence of these neurological outcomes comparing pre-specified risk intervals following vaccination with reference period. The risk intervals considered were 42 days for GBS and encephalitis/encephalomyelitis, and 60 days for Bell's palsy. Subgroup analyses were conducted by age (<60 and ≥60 years) and sex [1].
Results: Nearly 12 million of inhabitants (20% of Italian population), there were 706 events of GBS, 2,104 of Bell's palsy and 2,375 of encephalitis/encephalomyelitis. In the 42-day risk interval, there were 26 events of GBS and 135 events of encephalitis/encephalomyelitis; in the 60-day risk interval there were 124 events of Bell's palsy. There was no evidence of increased risk of GBS, Bell's palsy and encephalitis/encephalomyelitis, in main and in the subgroup analyses by age and sex. It is worth mentioning that in the previous Italian influenza vaccination campaign (2020/2021), an increased risk of GBS was found in the SCCS overall analysis and in the subgroup analysis of those aged ≥60 years [2].
Conclusion: Based on data collected during the 2021/2022 Italian influenza vaccination campaign, results from this large SCCS study indicated that influenza vaccination is not associated with GBS, Bell's palsy and encephalitis/encephalomyelitis.
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Use of artificial Intelligence-Based Assistant Tool: Quantitative and Qualitative Feedback from Pharmacovigilance Professionals of French Network of Pharmacovigilance Centers.

Francesco Salvo[1,2], Louis Létinier[3], Carole Baudry[3], Julien Juganous[3], Joelle Micallef[4], Guillaume Martin[3], Antoine Pariente[1], Laurent Chouchana[5]

[1]Université de Bordeaux, Bordeaux, France. [2]Chu de Bordeaux, Centre Régional de Pharmacovigilance Bordeaux-DROM, Bordeaux, France. [3]Synapse Medicine, Bordeaux, France. [4]Pharmacovigilance Centre, Department of Clinical Pharmacology and Pharmacovigilance, Marseille, France. [5]Regional Center of Pharmacovigilance, Pharmacology Department, Cochin Port Royal University Hospital, Paris, France

Introduction: Artificial Intelligence (AI)-based tools hold significant promises in Pharmacovigilance (PV), particularly in streamlining repetitive tasks related to Individual Case Safety Reports (ICSRs) management (1).
In France, a system known as Medication Shield, utilizing natural language processing, was developed and successfully tested to predict Adverse Events codes and seriousness (AE) (2,3). Medication Shield was officially implemented in 2021 to assist pharmacovigilance professionals (PVPs) within the French Network of Pharmacovigilance Centers (FNPVC) during the massive reporting wave related to post COVID-19 vaccines AE. However, despite its widespread use, PVPs feedbacks on its use and perceived utility were not yet properly evaluated.
Aim/Objective: Understand PVPs' perception of the Medication Shield AI-based tool and gather insights regarding its future development.Understand PVPs' perception of the Medication Shield AI-based tool and gather insights regarding its future development.
Methods: All PVPs affiliated to one of the 30 FNPVC (around 100 PVPs) were invited to participate in a qualitative survey. Questions concerned the current tool functioning, their perceived utility of AI for PV tasks, preferences regarding the tool future evolution, and suggestions for improving the interface tool. Additionally, a complementary survey was offered to ten PVP.
Results: A total of 58 responses were received from 26 Centers. While the understanding of AE coding proposals was generally high, only three PVPs accurately known the score of action of the AI. AI was considered useful or highly useful for proposing AE coding by 66% of respondents; this dropped to 47% considering the seriousness coding. Participants noted that AI could streamline ICSRs management, particularly for known and non-serious AE, thereby freeing time for the evaluation of more complex or atypical cases. PVPs emphasized the importance of human validation in the PV context, where expert assessment is crucial. They also highlighted the necessity for future developments to be user-centered and the importance of rigorous performance evaluation to enhance users trust.
Additionally, respondents suggested the implementation of a "*confidence degree*" for AE coding proposals to assist PVPs in selecting the most appropriate codes and to provide insights into how the tool operates. Finally, 30% of PVPs expressed concerns about potential human resource reductions in PV.
Conclusion: Conclusions The proposed AI tool was widely accepted within FNPVC, especially as a support for reducing workload in tasks of low added-value as the managing of expected non-serious AE. The successful implementation of new models, such as large language models, will require to collect and consider user needs and expectations needs and expectations of PVPs.
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Enhancing Detection and Reporting of Medication Errors Through Online Learning. Can an Online Course Bring About Any Actual Change?

Magnus Ekelo[1], Hager Ben Mosbah[1], Loubna Alj[2], Rita Benabdallah[2]

[1]Uppsala Monitoring Centre, Uppsala, Sweden. [2]Centre AntiPoison et de Pharmacovigilance du Maroc, Rabat, Morocco

Introduction: Medication error reports are a cornerstone of patient safety work and pharmacovigilance centres should be equipped to handle, analyse, and take actions on these reports[1]. Yet, the number of medication error reports reaching VigiBase is low, particularly in low and middle income countries[2].
To address this issue, we believe further education on medication errors, how to detect them, report them, and analyse them, is necessary. Uppsala Monitoring Centre (UMC) and the Centre AntiPoison and the Pharmacovigilance du Maroc (CAPM) has created an instructor-led course to serve as a pilot for evaluating the impact of education on medication error reporting.
Aim/Objective: To assess the impact of the online instructor-led course on the reporting of medication errors and assessments of reports in the participating countries.
Methods: A five-week online course was planned, organised, and offered to members of the WHO Programme for International Drug Monitoring on UMC's learning management platform[3]. Content covered topics from identification and reporting medication errors, to analytical tools for root cause analysis and risk minimisation actions. This course was designed with practicality in mind, incorporating assignments based on real-world cases and live discussions focused on application.
Before and after the course, participants conducted self-assessments of their understanding of seven principal topics covered in the course. Upon completion of the course, all participants were asked through a questionnaire what impact they thought the course had on their work with medication errors in daily practice.
Results: In total, 24 participants representing 14 countries completed the five-week course, and all participants completed the subsequent questionnaire. Among participants, 91% affirmed their intention to integrate course-derived knowledge into modifications of routines and practices within their respective centres. Most respondents (71%) answered that they would update SOPs and routines for medication error reports. The self-assessment results indicate improvements in the skills of participants in handling medication error reports.
Qualitative feedback revealed an intention to engage with healthcare professionals to increase awareness, as well as improve coding practices for medication error reports. Several centres planned to revise their protocols and routines, suggesting an initial positive impact of the course on operational practices.
Conclusion: Our findings suggest that a practically oriented online course can impact the way pharmacovigilance centres work with medication errors. Moreover, an online course could be an effective tool in enhancing the skills of pharmacovigilance professionals and in encouraging pharmacovigilance centres to reassess and modify their approaches to medication error report management.
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Pharmacological Therapy in Patients with Gender Dysphoria: A Cohort Study in the Lazio Region, Italy

Valeria Belleudi[1], Sara Lopes[1], Michela Servadio[1], Arianna Bellini[2], Marina Davoli[2], Antonio Addis[2]

[1]Department of Epidemiology, Lazio Regional Health Service, Roma, Italy. [2]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy

Introduction: Gender dysphoria is a condition characterized by intense and persistent distress caused by identifying with a gender different from one's sex assigned at birth. Therapy aims to reduce or eliminate this distress and involves various professionals, including psychologists, psychiatrists, endocrinologists, and surgeons. Pharmacologically, significant use of medications that affect both the hormonal and psychological spheres is expected.
Aim/Objective: To identify a cohort of patients with gender dysphoria and investigate the use of medications in this population.
Methods: Through the health information systems of the Lazio Region, a cohort of individuals with incident hospitalization for gender dysphoria (ICD-9-CM codes 302.85; 302.6) between 2011 and 2021 was identified. Starting from the index date (date of discharge from hospitalization), medication use was analyzed in the following year to identify the most frequently prescribed therapies. The therapeutic pattern was stratified based on sex assigned at birth.
Results: A total of 365 subjects with incident gender dysphoria diagnosis were identified: 46.8% had a male sex assigned at birth (MAB) and 53.2% had a female sex assigned at birth (FAB). The median age at the index date was 26 years: 26.3% were under 20 years old, 34.3% were between 20 and 30, and 39.4% were over 30 years old. In the youngest age group, MAB was prevalent (65%). In 10% of cases (n = 36), there was genital surgery during the index hospitalization (8.2% in MAB and 11.3% in FAB). In the year following the index date, 72% of subjects had at least one drug dispensation (MAB: 82%; FAB: 63%). Among users, the most frequently used drugs were: 50% antifungals (ATC J), 49% genitourinary system and sex hormones (ATC G), 40% gastrointestinal and metabolic system (ATC A), and 24% central nervous system. Excluding antifungal drugs, the three most prescribed drug classes among MAB were: anti-androgens (46%), estrogens (42%), and mineralocorticoid receptor antagonists with anti-androgenic properties (23%). While in FAB, they were: estrogens (20%), vitamin D (20%), and thyroid preparations (11%). Testosterone use, reimbursable by the National Health Service (NHS) starting from September 2020, involved 8% of FAB subjects. The use of antidepressants was 9% in MAB and 12% in FAB.
Conclusion: The study highlights widespread use of medications in managing gender dysphoria. Particularly, significant differences in therapeutic patterns emerged between MAB and FAB subjects. Further research is needed to compare these patterns with those of the general population and to fully understand the short- and long-term impact of pharmacological therapies on the quality of life of patients with gender dysphoria.
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Dual Orexin Receptor Antagonists Versus Z-drugs: a Disproportionality Analysis Using WHO Drug Safety Database

Giuseppe Cicala[1], Christophe Gauld[2,3], Jean-Arthur Micoulaud-Franchi[3,4], Francesco Salvo[5,6]

[1]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy. [2]Child Psychiatric Department, University Hospital of Lyon, F-69000, Lyon, France. [3]UMR CNRS 6033 SANPSY, University Hospital of Bordeaux, F-33076, Bordeaux, France. [4]University Sleep Clinic, University Hospital of Bordeaux, Place Amélie Raba-Léon, 33076, Bordeaux, France. [5]CHU de Bordeaux, Service de Pharmacologie Médicale, Centre Régional de Pharmacovigilance de Bordeaux, F-33000, Bordeaux, France. [6]Université de Bordeaux, INSERM, Bordeaux Population Health, U1219, F-33000, Bordeaux, France

Introduction: Insomnia medications can help in the management of sleep disorders and favour sleep health. Recently, Dual Orexin Receptor Antagonists (DORA) were marketed with indications of use similar to Z-drugs. However, their safety profile in a real-life setting is still largely unknown.

Aim/Objective: This study aims to analyse the real-world safety profile of DORAs and compare it with the one observed for Z-drugs, using data from the WHO Individual Case Safety Reports (ICSRs) database.

Methods: ICSRs collected in Vigibase between its inception and 01/09/2023, presenting as suspected or interacting drugs DORAs (suvorexant, lemborexant or daridorexant), or Z-drugs (zaleplon, zolpidem, zopiclone, eszopiclone) were evaluated. Characteristics of cases were first described, then quantitative differences between DORA and Z-drugs were assessed using reporting odds ratios (RORs) and 95% confidence intervals (CIs) as measures of disproportionality. Possible Adverse Drug Reactions (ADRs) were evaluated as Preferred Terms (PT) and Standardized MedDRA Queries (SMQs) of the MedDRA dictionary. Class disproportionalities were further assessed considering each DORA individually compared to the Z-drugs.

Results: Data regarding 82,043 ICSRs were retrieved, 9,669 related to DORA, and 72,374 related to Z-drugs. When compared to Z-drugs, DORA ICSRs showed a higher frequency of women (n = 5,415; 62.8% vs n = 41,175; 60.6%), but most importantly, older patients: 64 to 74 years 23.1% vs. 16.3%; $\geq$75 years 23% vs. 18.1%, in DORA and Z-drugs respectively. A total of 109 positive ROR values were found; the most frequent and disproportional ADRs were drug ineffective (n = 2,996; ROR = 3.3; 95% CI [3.1, 3.5]), nightmare (877; 6.8; [6.2, 7.4]), abnormal dreams (668; 11.7; [10.4, 13.2]), somnolence (630; 1.1; [1.0, 1.2]), and headache (486; 1.7; [1.5, 1.9]). Any meaningful differences were confirmed among individual DORAs, except for Lemborexant which was the only one significantly related to somnolence (n = 41; ROR = 1.7; 95% CI [1.2, 2.3]). Regarding SMQs, Lack of efficacy and medication errors were disproportional (ROR = 3.3; [3.1, 3.4] and 1.7; [1.5, 1.8], respectively). While depression and suicide/self-injury were not disproportional for all DORAs. The ROR for lack of efficacy was found positive for every DORA, while the ROR for medication errors was positive for suvorexant and daridorexant.

Conclusion: The present data show slight differences in the safety profile of DORAs compared to Z-drugs. Nightmares and headaches, which could worsen patient sleep quality, and the disproportional reporting of lack of efficacy merit further investigation. This analysis does not suggest potential signals concerning depression or suicidality.

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Sex differences in Beta-Blocker-Related Adverse Events: A Pharmacovigilance Comparative Analysis of Metoprolol and Carvedilol in Heart Failure Using EudraVigilance Data

Cecilia Cagnotta[1,2], Mario Gaio[1,2], Rosanna Ruggiero[1,2], Federica Fraenza[1,2], Liberata Sportiello[1,2], Concetta Rafaniello[1,2], Annalisa Capuano[1,2]

[1]Campania Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Naples, 80138, Italy. [2]Section of Pharmacology "L. Donatelli", Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, 80138, Italy

Introduction: Women are 1.5 more likely than men to have adverse events (AEs) [1]. Although sex differences in cardiovascular medicine are well known and findings from clinical practice suggest that a sex-specific recommendations should be addressed, the approach of heart failure (HF) guidelines remains sex-neutral [2].

Aim/Objective: To determine if sex appears to modify the safety of metoprolol and carvedilol in chronic HF by using data from a pharmacovigilance database (EudraVigilance, EV).

Methods: Data on Individual Case Safety Reports (ICSRs) of AEs by metoprolol or carvedilol were retrieved from the EV (2003-2022). We provided a descriptive analysis of the characteristics of ICSRs (AEs were categorized as System Organ Classes (SOCs)), stratifying data by sex and treatment. We used the reporting odds ratio (ROR) with a 95% of confidence interval to investigate disproportional reporting of each SOC between metoprolol and carvedilol in women and men with HF.

Results: 31,164 ICSRs including metoprolol or carvedilol as suspected drug were retrieved from EV and only 2,056 ICSRs reported sex information of patients with HF. More than half of the ICSRs was related to men aged 65-85 years. Both in women and men, carvedilol was reported more than metoprolol and the most reported serious AEs were related to carvedilol. AEs were mostly related to the SOC Cardiac disorders (women: 17.5% vs man: 17.7%). In both cohorts, the ROR indicates a statistically significant ($p < 0.05$) lower risk of reporting AEs for metoprolol in the SOC Investigations (ROR: women 0.49 (0.36-0.67) vs men 0.74 (0.59-0.93)) and Respiratory disorders (ROR: women 0.65 (0.46-0.90) vs men 0.48 (0.30-0.64)). Metoprolol was associated with a higher reporting risk in women for gastrointestinal (ROR: 1.45 (1.08-1.95)) and psychiatric disorders (ROR: 1.92 (1.30-2.83)), while no treatment difference was observed in men. Metoprolol was associated with a lower reporting risk in men for Blood and lymphatic system disorders (ROR: 0.54 (0.31-0.90)), Metabolism disorders (ROR: 0.56 (0.39-0.81)), while no treatment difference was observed in women.

Conclusion: Our study suggested a disparity between metoprolol and carvedilol in HF patients. Considering limitations, our study provides valuable insights, emphasizing the need for further research to refine treatment recommendations for HF patients.

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Intoxicating Novel Cannabinoid Products Involved in Adverse Event Reports Received by the Food and Drug Administration

Michelle Hines, Scott Janiczak, Cassandra Taylor, Monica Muñoz, Lisa Wolf

U.S. Food and Drug Administration, Silver Spring, USA

Introduction: The passage of the Agriculture Improvement Act of 2018 (Public Law 115-334, also referred to as "the 2018 Farm Bill") removed hemp, defined as cannabis and derivatives or extracts of cannabis having not more than 0.3 percent delta-9 tetrahydrocannabinol (Δ9-THC) by dry weight, from Schedule I controls in the Controlled Substances Act. Shortly afterward, delta-8 THC (Δ8-THC) emerged in the cannabis marketplace purporting to be a "2018-Farm-Bill-compliant" substitute for Δ9-THC, followed by numerous intoxicating cannabinoids with limited safety data (i.e., "novel cannabinoids").
Aim/Objective: To provide a description of intoxicating novel cannabinoid products conveyed in adverse event reports received by the U.S. Food and Drug Administration (FDA).
Methods: We searched the FDA Adverse Event Reporting System (FAERS) database for domestic adverse event reports submitted directly to FDA with novel-cannabinoid-containing products from January 1, 2019, through March 31, 2024. We abstracted product information and outcomes from report narratives and coded fields; furthermore, we reviewed product descriptions on cannabis retail marketplace websites, when possible.
Results: We identified 40 reports describing adverse events with products reportedly containing 1 or more of the following 14 novel cannabinoids: tetrahydrocannabiphorol (THCP) (n = 14), THC acetate (THC-O-acetate) (n = 12), Δ10-THC (n = 10), hexahydrocannabinol (HHC) (n = 8), tetrahydrocannabihexol (THC-H) (n = 8), THC-C8 (THC-JD) (n = 6), hexahydrocannabiphorol (HHCP) (n = 3), tetrahydrocannabutol (THC-B) (n = 2), Δ8-THCP (n = 1), Δ11-THC (n = 1), 11-hydroxy-THC (n = 1), HHC acetate (HHC-O-acetate) (n = 1), tetrahydrocannabinolic acid (THCA) (n = 1), or mixture of Δ8-THC esters (n = 1). Thirty-one reports (78%) had products containing novel cannabinoids co-formulated with the intoxicating cannabinoids Δ8-THC (n = 29) or Δ9-THC (n = 6). Of the 40 reports, 37 (93%) were coded with a serious outcome (per 21CFR314.80); furthermore, 18 (45%) were either hospitalized (n = 8) or went to the emergency department (n = 10) following the event. A total of 14 products (35%) contained 3 or more intoxicating cannabinoids (median number of intoxicating cannabinoids, 2; range, 1 to 9). The most frequently reported formulations were gummy (n = 24; 60%) and vape (n = 10; 25%). Among 22 gummy products with cannabinoid content information available, 9 (41%) reportedly contained ≥200 mg cannabinoids per single gummy (median, 125 mg; range, 50 to 750 mg).
Conclusion: FDA has received adverse event reports, including reports with serious outcomes, that describe a variety of intoxicating novel cannabinoids that have limited regulatory oversight and are available for purchase in the cannabis retail marketplace. The novel cannabinoid products implicated in the reports largely contain high doses of multiple intoxicating cannabinoids.
References
Disclaimer: This abstract reflects the views of the authors and should not be construed to represent FDA's views or policies.

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Association Between Anti-PD-1/PD-L1 Drugs and Hearing Impairment

Aurore Morel, Maxime Moiny, Brahim Azzouz

Regional Centre for Pharmacovigilance, Reims University Hospitals, Reims, France

Introduction: Anti-PD-1/PD-L1 drugs are associated with immune-related adverse events. However, the knowledge about ototoxicity is limited. We found a few articles in the scientific literature describing hearing disorders with anti-PD-1/PD-L1 agents, particularly with nivolumab and pembrolizumab. [1-4]
Aim/Objective: We aimed to characterize hearing impairment with anti-PD-1/PD-L1 drugs and to perform on the disproportionality analysis using the World Health Organization (WHO) pharmacovigilance database (VigiBase).
Methods: Data were extracted from VigiBase until 31 March 2024 using the sub-search Standardized MedDRA Query (SMQ) "Hearing impairment" and the ATC (Anatomical Therapeutic Chemical) class L01FF. We characterized the patients, and reactions, and we performed disproportionality analysis by calculating the reporting odds ratio (ROR) and its 95% confidence intervals (CIs).
Results: Of the 172,002 reports of anti-PD-1/PD-L1 agents as suspected/interacting drugs in VigiBase, we found 629 hearing impairment reactions in 599 patients. The mean age was 64.9 ± 12.8 years and 55.9% were men. The most involved anti-PD-1/PD-L1 were nivolumab and pembrolizumab (n = 316; 52.5% and n = 182; 30.2%, respectively). The most co-suspected drug was ipilimumab (n = 146). The most frequent adverse effects in the sub-search SMQ "Hearing impairment" were facial paralysis (n = 155, 24.6%), tinnitus (n = 107, 17%), hypoacusis (n = 102, 16.2%) and deafness (n = 93, 14.8%). Of the total reported cases of hearing impairment reactions, 190 (30.2%) had recovered/recovered with sequelae/recovering outcome. The vast majority of cases are serious (83.8%). No significant safety signal was found in the sub-search SMQ "Hearing impairment". For adverse events at the Preferred Term (PT) level, we found several significant signals, including deafness bilateral with pembrolizumab (ROR = 5.2, 95% CI 3.1-8.7) and nivolumab (ROR = 3.2, 95% CI 1.8-5.6); deafness neurosensory with nivolumab (ROR = 3.1, 95% CI 2.1-4.6). The median time to onset was 30.4 days for neurosensory deafness and deafness bilateral with nivolumab, and 197.7 days for deafness bilateral with pembrolizumab.
Conclusion: The literature describing hearing impairment with anti-PD-1/PD-L1 drugs and the significant signals of deafness bilateral with pembrolizumab and nivolumab and deafness neurosensory with nivolumab highlight the need to sensitize physicians, particularly oncologists and otolaryngologists. However, pharmacoepidemiologic studies are needed to assess the existence of a causal relationship and incidence.
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Safety Signal Identification for Risankizumab-rzaa in the Sentinel Distributed Database Using Self-Controlled and Active Comparator Study Designs

Leah B. Herity[1], Geetha S. Iyer[2], Jillian Burk[2], José J. Hernández-Muñoz[1], Jummai Apata[1], Monica A. Muñoz[1], Judith C. Maro[2,3], Derek Campbell[2], Nora P. McElroy[2], Megan Wiley[2], Joy Kolonoski[2], Ashley I. Michnick[2,3]

[1]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA. [2]Harvard Pilgrim Health Care Institute, Boston, MA, USA. [3]Harvard Medical School, Boston, MA, USA

Introduction: Application of tree-based scan statistics (TreeScan®) to the Sentinel Distributed Database (SDD) allows for untargeted safety signal identification using a hierarchical outcome tree with simultaneous adjustment for multiple scanning of correlated outcomes. TreeScan® analyses may be implemented using self-controlled risk interval (SCRI) or active comparator (AC) designs. Risankizumab-rzaa, FDA-approved in 2019, is an IL-23 inhibitor currently indicated for plaque psoriasis, psoriatic arthritis, and Crohn's disease.

Aim/Objective: To detect new potential safety signals following the initiation of risankizumab-rzaa using both SCRI and AC study designs.

Methods: We conducted two TreeScan® signal identification studies in non-pregnant adult risankizumab-rzaa new users (defined as no use in the prior 183 days) in the SDD. For the SCRI study, we constructed two cohorts for primary analyses: fixed risk window (Risk: 1 to 28 days post-index; Control: 56 to 29 days pre-index) and variable risk window (1 to 183 days post-index). For the AC study, we used high-dimensional propensity scores (hdPS) to match risankizumab-rzaa new users 1:1 to the IL-23 inhibitor guselkumab, observing outcomes through 183 days post-index. In both study designs, we identified incident outcomes from an ICD-10-CM hierarchical tree in inpatient and emergency department settings to identify imbalances in outcome timing (SCRI study) or occurrence (AC study) rising to the level of statistical significance ($p \leq 0.05$).

Results: The SCRI study included 28,684 and 20,345 new users in the fixed risk window and variable risk window cohorts, respectively. Users were on average 51.7 years of age at index, with over 97% having evidence of plaque psoriasis and 13% with prior use of anti-TNF biologics. There were no statistical alerts in the fixed risk window cohort; in the variable risk window cohort, we identified a statistical alert for cholelithiasis without cholecystitis on days 9 to 11. The AC study included 14,819 risankizumab-rzaa new users matched to guselkumab. The matched users were largely similar to the SCRI cohorts. We identified no statistical alerts in the AC study.

Conclusion: We demonstrate the feasibility of using two different untargeted signal identification study designs to identify safety signals for risankizumab-rzaa. Monitoring tens of thousands of new users for thousands of outcomes, we found few statistical alerts across both study designs. Although we may be underpowered to detect rare adverse events, we have provided valuable reassurance of risankizumab-rzaa's short-term safety profile.

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Post-Marketing Surveillance of Polatuzumab Vedotin: A Disproportionality Analysis of the US FDA Adverse Event Reporting System (FAERS) Database

Claudia Muscarà[1], Alessandro Allegra[2], Marco Tuccoli[3], Alessandra Flaccavento[4], Paola Maria Cutroneo[1]

[1]Sicilian Regional Pharmacovigilance Center, Clinical Pharmacology Unit, University Hospital of Messina, Messina, Italy. [2]Hematology Unit, Department of Human Pathology in Adulthood and Childhood "Gaetano Barresi", University of Messina, Messina, Italy. [3]Unit of Adverse Drug Reactions Monitoring, University Hospital of Pisa, Pisa, Italy. [4]Department of Clinical and Experimental Medicine–Section of Pharmacology and Pharmacovigilance, University of Pisa, Pisa, Italy

Introduction: The antibody-drug conjugate polatuzumab vedotin (POLIVY®), a CD79b-directed antibody and microtuble inhibitor conjugate, was recently granted and is becoming increasingly available for onco-haematological patients, therefore the need to monitor its post-marketing safety profile is emerging.

Aim/Objective: This study aims to better characterize the post-marketing safety profile of polatuzumab vedotin, analyzing spontaneous suspected adverse drug reaction (ADR) reports reported into the US FDA Adverse Event Reporting System (FAERS) database, focusing on identified serious and unexpected adverse events, especially concerning immune system, cardiovascular and gastrointestinal disorders and second primary neoplasms.

Methods: All spontaneous suspected ADR reports related to polatuzumab vedotin were selected from the US FAERS database (period: January 2004–September 2023). Descriptive and disproportionality analyses (reporting odds ratio - ROR) were performed by comparing polatuzumab vedotin with all other drugs in FAERS database (reference group 1- RG1). ADR notoriety was assessed through package insert.

Results: Overall, 4806 reports related to polatuzumab vedotin were identified. The majority of reports concerned male and elderly patients. The most reported adverse events, classified by MedDRA Preferred Terms, for polatuzumab vedotin were disease progression [N = 1281], neutropenia [N = 316], COVID-19 [N = 305], drug ineffective [N = 294], LDH increased [N = 291], pyrexia [N = 271], anemia [N = 257], and febrile neutropenia [N = 231]. Signals of disproportionate reporting (versus RG1) confirmed known adverse drug reactions and highlighted also unexpected adverse events, including second primary neoplasms (e.g. abdominal neoplasm, melanoma, meningioma), cardiovascular disorders (e.g. arrhythmia, cardiac failure, fibrillation, valve incompetence, thromboembolism), gastrointestinal disorders (e.g. intestinal obstruction/ileus, GI perforation, pancreatitis) and immune-related disorders (e.g. cytokine release syndrome, hypogammaglobulinaemia, graft versus host disease, sarcoidosis).

Conclusion: This study confirms the presence of well-known adverse reactions and detects potentially emerging safety issues related to polatuzumab vedotin, including cardiovascular disorders, gastrointestinal disorders, immune-related disorders and the development of new primary tumors, which require further investigation.

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Selective Serotonin Reuptake Inhibitors and Venous Thromboembolism: a Pharmacovigilance Analysis of the Eudravigilance Database

Andreia Lopes[1,2], Luísa Prada[1,2], Rita Avó-Baião[1,2], João Fernandes[3], Márcia Silva[3]

[1]*Clinical Pharmacology Unit, Santa Maria Local Health Unit, Lisbon, Portugal.* [2]*Clinical Pharmacology ans Therapeutics Lab, Faculty of Medicine Of University of Lisbon, Lisbon, Portugal.* [3]*Directorate for Risk Management of Medicines, INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon, Portugal*

Introduction: To assess and characterize the suspected VTE adverse drug reactions (ADR) reported to the EudraVigilance (EV) database regarding SSRI.Venous thromboembolism (VTE), comprising pulmonary embolism and deep venous thrombosis, is a common preventable condition associated with high morbidity and mortality. [1, 2] Selective serotonin reuptake inhibitors (SSRI) are widely used as a first-line pharmacological treatment of depression and anxiety disorders, whose prevalence has been rising, increasing SSRI consumption. [3, 4] Despite conflicting evidence, some studies suggest an association between SSRI and VTE risk. [5, 6] However, to our knowledge, no study has specifically explored this possible association using pharmacovigilance databases.

Aim/Objective: To assess and characterize the suspected VTE adverse drug reactions (ADR) reported to the EudraVigilance (EV) database regarding SSRI.

Methods: Retrospective analysis of Individual Case Safety Reports (ICSR) received in the EV database from 1st January 2014 until 31st December 2023, regarding SSRI encompassed by the Anatomical Therapeutic Chemical code N06AB, containing at least one ADR belonging to the Standardized MedDRA Query "Embolic and thrombotic events, venous". ICSR were stratified by age and gender, suspected medicinal products, MedDRA Preferred Term (PT), and seriousness of outcome.

Results: In total, 339 ICSR were retrieved. Escitalopram was the most reported SSRI (n = 105; 31%), followed by sertraline (n = 87; 25.7%) and fluoxetine (n = 53; 15.6%); fluvoxamine was the least reported (n = 12; 3.5%). Most of the ICSR referred to women (n = 210; 61.9%) and patients between 18 and 64 years old (n = 187; 55.2%). Only one ICSR was reported as non-serious, and 44 (13.0%) reported deaths. Ninety-one ICSR (26.8%) had an SSRI as the only suspected drug. A median of three suspected/interacting drugs *per* - ICSR was found. The most reported PT terms were "Pulmonary embolism" and "Deep vein thrombosis", in 197 (58.1%) and 109 (32.2%) ICSR, respectively.

Conclusion: This study provided an overview of EV reports on suspected SSRI-induced VTE. However, the unavailability of consumption data on SSRI and underreporting precludes any definite conclusions regarding the true frequency of these suspected AD. Furthermore, since the associations found were based on incomplete clinical data, no causality assessment can be performed, and the results should be considered preliminary and interpreted cautiously. Previous studies suggested that increased VTE risk may be related to the depression itself and not to the treatment. [7] However, in a substantial number of cases the causes of VTE are unknown. [8] Future prospective studies are required to explore why this class of drugs appears associated with VTE events in pharmacovigilance databases.

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Safety of RSV Vaccine among Pregnant Individuals: A Real-World Pharmacovigilance Study Using Vaccine Adverse Event Reporting System

Abdallah Alami[1], Santiago Perez-Lloret[2,3,4], Donald Mattison[1,5]

[1]*School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada.* [2]*Consejo Nacional de Investigaciones Cientificas y Técnicas (CONICET), Buenos Aires, Argentina.* [3]*Observatorio de Salud Pública, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina.* [4]*Department of Physiology, Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina.* [5]*Risk Sciences International, Ottawa, Canada*

Introduction: In August 2023, the FDA authorized the first RSV vaccine (RSVPreF) for pregnant women in the USA, amid clinical trial observations suggesting a numerical but not statistically significant increase in preterm births, raising concerns that necessitated further monitoring to ensure vaccine's safety [1–4].

Aim/Objective: To describe the post-marketing safety of RSVPreF among pregnant individuals.

Methods: This case series study analyzed adverse event (AE) reports submitted to the Vaccine Adverse Event Reporting System (VAERS) database following RSVPreF immunization from September 1, 2023, to February 23, 2024. Descriptive statistics were used to assess all AE reports with RSVPreF, including frequency, gestational age at vaccination, time to AE onset, reported outcomes, and proportion of serious reports. Bayesian Confidence Propagation Neural Network (BCPNN) was utilized, estimating the information component (IC) to identify disproportionate reporting of RSVPreF–event pairs. Reports of preterm births were clinically reviewed.

Results: VAERS received 77 reports pertaining to RSVPreF vaccination in pregnant individuals, with 42 (54.55%) classified as serious. Associated with these reports, a total of 211 suspected AE terms linked with RSVPreF vaccine were documented. The most commonly reported non-pregnancy-specific AEs included headache, injection site erythema, and injection site pain, each noted in 3.8%, 3.8%, and 2.8% of reports, respectively. For pregnancy-specific AEs, preterm birth was most frequently reported at 12.8%, followed by AE terms such as preterm premature rupture of membranes and cesarean

section, each at 3.3%, and cervical dilatation, hemorrhage during pregnancy, and uterine contractions during pregnancy, each at 1.4%. Our disproportionality analysis indicated a significant signal for various AEs, particularly highlighting preterm birth with an IC of 2.18 (95% CI, 1.54-2.63), suggesting that reports of preterm birth associated with RSVPreF vaccination occurred more frequently than statistically expected. Most of the reported preterm births were moderate to late, occurring between 32 and less than 37 weeks of gestation. The median time from immunization to the onset of preterm birth was 3 days, with two-thirds of the cases reported within a week of vaccination.

Conclusion: While reported AEs were generally consistent with the safety profile observed in prelicensure studies, this analysis underscores the ongoing concern about persistent safety signal for preterm birth among pregnant individuals following RSVPreF vaccination. Comprehensive longitudinal follow-up, including prospective pregnancy registries and infant follow-up studies is urgently required.

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Preparing for Vaccine Adverse Event of Special Interest-X (AESI-X): a standardized approach applied to novel vaccines

Barbara Law[1], Dale Nordenberg[1,2], Eileen Farnon[1,3], Andy Stergachis[1,4], Rebecca Chandler[5], Robert Chen[1,3]

[1]Safety Platform for Emergency vACcines (SPEAC) Project, Decatur, USA. [2]Thriive.AI, New York, USA. [3]Brighton Collaboration, Task Force for Global Health, Decatur, USA. [4]University of Washington, Seattle, USA. [5]Coalition for Epidemic Preparedness Innovations, Oslo, Norway

Introduction: Through the Coalition for Epidemic Preparedness Innovations (CEPI)-funded SPEAC project, the Brighton Collaboration (BC) creates tools to facilitate standardized safety assessments for novel vaccines under development targeting pandemic-prone pathogens including "Disease X." Inherent to CEPI's mission to provide vaccines within 100 days of a pandemic is ensuring preparedness for novel "AESI-X" associated with these new vaccines. When an AESI-X emerges, many teams quickly develop case definitions. Real-time harmonization of case definitions is challenging due to lack of surge capacity, data for decision making, and global coordination. This heterogeneity can result in lack of comparability across vaccine safety surveillance systems.

Aim/Objective: To facilitate development of a process among key vaccine safety stakeholders for developing a standardized CD for an AESI-X prior to its emergence.

Methods: We reviewed BC process and experience for developing standardized CD for > 70 AESIs since our inception in 2000, and identified possible categories of AESI-X and solutions to facilitate rapid CD development during the emergence of an AESI-X.

Results: Three categories of AESI-X were identified that we would need to prepare for in the future:

Category of AESI-X	'Known-Known'	'Known-Unknown'	'Unknown-Unknown'
EVENT	WELL-DEFINED	WELL-DEFINED	NEW ENTITY
Prior proven vaccine association	Yes	No	No
Prior case definition for vaccine safety	Yes	Possible if a previously prioritized AESI	No
Examples	Myocarditis following COVID-19 mRNA vaccines.	1. Narcolepsy following adjuvanted 2009 pandemic H1N1 vaccines 2. Sensorineural Hearing Loss for Lassa vaccines	1. Atypical measles after inactivated measles vaccine 2. Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) following COVID-19 adenoviral vectored vaccines

We created a checklist for CD preparation to investigate whether 1) a BC CD already exists and may need to be revised; 2) other CDs have been developed for safety surveillance; 3) an expert consensus CD exists; 4) a diagnostic gold standard test exists; 5) existing datasets may be used to validate a CD; 6) other clinical events exist that overlap with the new syndrome; and 7) expert clinicians and researchers are willing to participate in a CD work group.

Conclusion: Creating a process to develop BC CDs for future AESI-X is a key component of pandemic preparedness to facilitate the implementation of novel vaccines. The three categories of AESI-X and checklist provide the necessary baseline information for BC to facilitate a conversation with other key vaccine safety stakeholders to arrive at a consensus process, ideally ahead of the next AESI-X. As with all pandemic processes, implementation, evaluation, and subsequent improvement will be needed.

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Enhancing Local Literature Screening in Pharmacovigilance with an Automated Approach

Artem Horilyk

Danylo Halytsky Lviv National Medical University, Lviv, Ukraine. DrugCards OU, Lviv, Ukraine

Introduction: Pharmacovigilance plays a crucial role in ensuring patient safety by identifying, analyzing, and preventing adverse events associated with the use of medicinal products. A significant challenge is the efficient extraction of valuable safety data from local medical literature that is not indexed in global databases. These sources are often overlooked yet contain critical safety information.

Aim/Objective: The aim of this study is to evaluate the effectiveness of an automated approach to screen local medical literature using the

DrugCard pharmacovigilance platform, which we designed specifically for this purpose.

Methods: Our current analysis included all medical and pharmaceutical journals published locally in Ukraine throughout 2023. We selected 100 non-indexed journals, including those recommended by the local competent authority, and tracked their factual publication frequency weekly from January 1 to December 31, 2023.

Results: The publication frequency varied significantly across the 513 new issues published within the year, with periodicity ranging from 1 to 40 issues per journal per year. Per week analysis of publication frequency revealed considerable variability: a minimum of 3 and a max of 21 new journal issues were published during a single week. This puts great pressure on a PV specialist to comply with timelines set for analysing the journals after the issue is published and reporting safety cases. Our designed solution for this problem is the DrugCard platform, which is a database of local non-indexed medical literature in a variety of languages. Over the past 2 years, we managed to enlarge the amount of local journals covered by 650 titles, and in April 2024 it covers around 800 valid local journals from 50 countries around Europe, MENA and CIS [1]. The use of the DrugCard platform significantly reduced the workload on pharmacovigilance specialists, who would otherwise need to review each publication manually. Initial tests using an AI-based large language model to identify safety data within the DrugCard database showed promising results in streamlining the extraction of safety information from a wide array of local journals regardless language they are published in.

Conclusion: Local literature is a valuable source of safety information though requires a lot of cost and human efforts. Automating the screening process for local non-indexed literature, including modern AI-technologies is essential to improve the cost/efficiency of this process and should be recommended as a best practice in global pharmacovigilance guidelines. The DrugCard platform represents a significant advancement in this area, demonstrating substantial benefits in efficiency and reliability.

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Analysis of ADR In Oncology Patients Treated With Fluoropyrimidines with Known and Unknown Genotype in Relation to DPYD Gene Polymorphisms

Arianna Bonaldo[1], ELENA BERTI[2], Erica Maccari[3], Marina Coppola[2]

[1]Department of Pharmaceutical Sciences, University of Padua, Padua, Italy. [2]Pharmacy Unit, Veneto Institute of Oncology - IOV IRCCS, Padua, Italy. [3]Department of Diagnostic and Public Health, Section of Pharmacology, University of Verona, Verona, Italy

Introduction: Fluoropyrimidines are a class of drugs widely used in oncology. 5-FU was the first compound [1]; capecitabine, an oral prodrug, was later developed [2]. Despite their proven efficacy, these medicines have a very narrow therapeutic index and predicting individual response to treatment and related toxicities is still a critical issue. Many studies investigated the role of the DPD enzyme, encoded by the DPYD gene, in their metabolism [3]. These studies led the Regulatory Agencies to issue recommendations, emphasizing both the importance of proper genetic screening and the need for dose reduction when specific types of polymorphisms are present.

Aim/Objective: To quantitatively and qualitatively estimate the ADRs induced by treatment with capecitabine (cohort C) and with 5-FU (cohort F) in patients with solid tumors both in relation to sociodemographic and clinical characteristics, and to possible DPYD gene polymorphisms.

To test the effectiveness of appropriate dose reduction in relation to the presence of any DPYD gene polymorphism as a prevention of the occurrence of ADRs.

Methods: This retrospective observational study involved two hundred patients with solid tumours who started capecitabine (cohort C) or 5-fluorouracil (cohort F) treatment between July 1, 2022 to December 31, 2022 at the Veneto Institute of Oncology in Padua, Italy. Sociodemographic data, medical history, genotype related to the DPYD gene, data regarding ongoing cancer treatment and related ADRs were collected from electronic medical records. The observational period covered 12 months. ADR data were analyzed for the total cohort, to be later compared between the two cohorts and with regard to DPYD gene polymorphisms. Patients were categorized by age, ECOG PS, and oncologic disease. ADRs severity was classified according to CTCAE criteria (vers. 5.0).

Results: The results showed that 187 patients (93,5%) experienced ADRs (n = 708), with an average of 3,8 ADRs per person. No significant numerical difference was observed between the two cohorts. ADRs of the gastrointestinal tract were the most frequent (n = 297), along with skin (n = 102) and hematologic ADRs (n = 74). Cardiotoxicity affected mostly patients in cohort F(n = 12), who reported to a much greater extent severe neutropenia (n = 28). Palmoplantar erythrodysesthesia appeared mostly in patients undergoing treatment with capecitabine (n = 38). No particular correlations were shown between the occurrence of ADRs and patient age or ECOG PS at the start of treatment. Patients treated with capecitabine for breast cancer experienced very few severe ADRs, while increased toxicity appeared for patients with pancreatic cancer. Most subjects were genetically screened for polymorphisms of the DPYD gene. Patients carrying the polymorphism (n = 7), who did not have more severe or major ADRs, were administered dose reductions according to the recommendations of the regulatory agencies.

Conclusion: The present study highlights the need to further investigate cardiac toxicities[4] and the correlation between oncological pathology and the occurrence of ADRs.

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Comparison of Different NLP Systems to Extract Adverse Drug Reaction Information from the Medicinal Product Information

Silvia Girotti[1], Giuseppe Cicala[2], Riccardo Lora[1], Francesco Salvo[3], Ugo Moretti[1]

[1]Dept of Diagnostic and Public Health, University of Verona, PV Centre of Veneto Region, Verona, Italy. [2]University of Messina, Messina, Italy. [3]Université de Bordeaux, Centre Régional de Pharmacovigilance Bordeaux-DROM, Bordeaux, France

Introduction: Adverse drug reactions (ADRs) are listed in Europe in the section 4.8 of the summary of product characteristics (SmPCs) of each approved medicinal product. No official database on the ADRs present in the SmPC classified with MedDRA (Medical Dictionary for Regulatory Activities) are present in Europe (1).
Aim/Objective: Aim of this paper is to compare the results of two NLP (Natural Language Processing) approaches used to create an ADR database for Italian and French drugs.Aim of this paper is to compare the results of two NLP (Natural Language Processing) approaches used to create an ADR database for Italian and French drugs.
Methods: Two different NLP approaches were used in France and in Italy. Twenty SmPCs of different products have been randomly extracted by the EMA repository. Each NLP system extracted the information on ADRs from the 4.8 section of the French and Italian versions of the same SmPC. ADRs were coded and compared with an Italian and French gold standard at MedDRA Preferred Term (PT) level. Results are given as true positives (TP, same PT in the gold standard) and false positives (FP, PT not present in the gold standard).
Results: A total number of 1,119 PTs were identified by French and 1,416 PTs by Italian NLPs vs French (1,370 PTs) and Italian (1,358 PTs) gold standards. TP were 85% in Italy (range 69-97) and 58% in France (range 27-77). FP were 19% in Italy (range 6-38) and 29% in France (range 15-51).
Differences between the two NLPs must be evaluated looking at the different approaches used. In Italy the system worked at PT level whereas in France the system coded also terms at High Level Terms (HLT) or High Level Group Terms (HLGT) that were not included in the analyses. For this reason in France the value of TP could be underestimated since many PT were recognized by the system at HLT or HLGT term. For example the HLGT Headaches instead of the PT Headache or the HLGT Angioedema and urticarias the HLT Angioedemas instead of PT Angioedema.

Two more issues must be considered evaluating the performance of the NLP systems. Due to the high MedDRA PT fragmentation a FP could be very close to the medical concept listed in the SmPC and could be considered TP. Moreover the layout of the information in the 4.8 section can be very different among the SmPCs. In many drugs a table summarize the ADR and a "Description of selected adverse reactions" is present below the table. Many FP are related to this section where for example indication of use or comorbidities are also listed.
Conclusion: NLP approaches are usable to create SmPCs databases, but that their performance must be analyzed looking at the used methodology.
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Strengthening Pharmacovigilance in Rwanda, Introducing PViMS for Spontaneous Reporting of Adverse Drug Effects

Lazzare ntirenganya[1], Emile Bienvenu[1], abimana Eugene Rwandenzi[2], Antoine Gatera[2], Kate Kikule[3], Nereah Kisera[4], Elizabeth Woldemariam Teketel[5], Kim Hoppenworth[3]

[1]Rwandan FDA, Kigali, Rwanda. [2]MTaPS, Kigali, Rwanda. [3]MTaPS, VA Arlington, USA. [4]MTaPS, Nairobi, Kenya. [5]MTaPS, Addis Ababa, Ethiopia

Introduction: Monitoring, reporting, and analysis of adverse events (AE) of newly introduced medicines, including vaccines, in real-life conditions are key components of PV and hence it was a high priority for Rwanda's Food and Drug Authority. As in many low- and middle-income countries (LMICs), PV in Rwanda remains weak. A 2018 World Health Organization assessment showed that the PV system did not meet minimum standards, and lack of an electronic system for data reporting, analysis, and management was a big challenge.
Aim/Objective: To address the gaps observed in AE data reporting, analysis and management and enhance monitoring drug safety.
Methods: The USAID MTaPS Program (2018–2024) assisted the MOH and the Rwanda Food and Drugs Authority (FDA) in introducing the use of an electronic online reporting tool, the PharmacoVigilance Monitoring System (PViMS). PViMS is a web-based application that allows for real-time reporting, recording, analysis and provision of feedback of data on AEs and AEFIs in a timely manner (1,2). It can also be used for both active and spontaneous PV surveillance and has the capacity to generate E2B format to transmit data directly into the WHO VigiFlow® system. MTaPS engaged in discussion with the Rwanda FDA's Division of PV and Safety Monitoring of Medical Products, provided training and advocacy to health workers, launched PViMS in June 2021, successfully advocated for hiring additional Information technology (IT) staff to support PViMS implementation and provided continuous support for the appropriate use of the tool. Recently, WHO GBT assessment ranked Rwanda FDA vigilance function operating at Maturity level 3 with the goal or attainment of WHO GBT Maturity level 4.
Results: From June 2021 to January 2023, a total of 1,431 AEs and AEFIs were reported through PViMS compared with the 385 general reports that Rwanda FDA had received using paper-based reporting from March 2018 to June 2021. This reflects reporting for Ebola and COVID-19 vaccines and other medicines. Of these, 670 were reviewed, of which 527 (including 467 related to COVID-19) were investigated by the Rwanda FDA and 46 serious AEFI were analyzed for causality by the National AEFI committee.
Conclusion: The Rwanda FDA uses data reported through PViMS to capture unexpected reactions and detection of safety signals to vaccines and other medicines and uses the data to make regulatory decisions for improved patient safety.
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219 Are Causal Claims Reported in Disproportionality Analysis Using Individual Case Safety Reports Exacerbated in Related Citations? A Meta-research Study

Claire BERNARDEAU[1], Bruno REVOL[1,2], Francesco SALVO[3,4], Michele FUSAROLI[5], Emmanuel RASHI[5], Jean-Luc CRACOWSKI[1,2], Matthieu ROUSTIT[2,6], Charles KHOURI[1,2,6]

[1]Pharmacovigilance Unit, Grenoble Alpes University Hospital, Grenoble, France. [2]Univ. Grenoble Alpes, Inserm U1300, HP2, Grenoble, France. [3]Medical pharmacology department, Bordeaux University Hospital, Bordeaux, France. [4]Bordeaux University, Inserm U1219, BPH, Team AHeaD, Bordeaux, France. [5]Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy. [6]Univ. Grenoble Alpes, Inserm CIC1406, Grenoble Alpes University Hospital, Grenoble, France

Introduction: Detection of new adverse drug reactions after drug marketing mainly relies on disproportionality analyses (DAs) using individual case safety reports databases. Previous meta-epidemiological studies have found considerable misinterpretation of the results from DAs, notably in overstating causal claims.
Aim/Objective: We aim to explore the consequences of causal wording used in abstracts of DA studies on the interpretation of results by other researchers, by analyzing related citations.
Methods: We selected the 30 DAs studies (source articles) with the highest Altimetric Attention Score (up to the 30/03/22), using the Altmetric explorer database. For each article, we extracted all related citations using Dimension database (citing studies). We assessed the level of causal statements in title and conclusion of the abstract of source articles, and in related citations based on a pre-determined 4-level scale (1/appropriate interpretation; 2/ambiguous interpretation; /3conditional causal; 4/unconditionally causal). Judgement about causal statement of all abstracts of source articles and citations was performed in parallel by 2 authors and discrepancies resolved among the team. We assessed the association between causal statements in sources articles and citing studies through multinomial regression models.
Results: Overall, 27%(n = 8) of source studies used unconditionally causal claims in their title and 30%(n = 9) in their abstract's conclusions; only 36%(n = 11) used appropriate claims in their title and 33%(n = 10) in their abstract's conclusions. Among the 622 citations analyzed, 285 (45.8%) used unconditionally causal claims when referring to the findings from DAs and only 164 (26.4%) used appropriate claims. The results of the multinomial models found that level of causal claims citations was positively associated with the level of causal claims in abstract conclusion of source articles (LogLRT $p<0.00001$), but not with the titles. The probability of citation containing unconditionally causal claims was 30.2% (95% CI 22.8%-37.6%) when referring to source articles using approportionate interpretation of their results, whereas it was 56.4% (95% CI 48.7%-64.2%) for source articles containing unconditionally causal claims in their conclusion. Inversely the marginal probabilities of citation using correct interpretation decreases from 40.7% (95% CI 32.7%-48.6%) to 22.6% (95% 16.0- 29.1%).
Conclusion: Stronger causal claims in abstract conclusions of DAs studies were associated with higher probability of causal claim in related citations. In addition, even when abstracts of DAs contained appropriate interpretation of the findings, a considerable part of citations by other researchers exaggerated causal claims.
References

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Landscape Assessment of Active Safety Surveillance of Novel Vaccines in Low- and Middle-Income Countries

Andy Stergachis[1], Esperanca Sevene[2], Alexander Precioso[3], Rebecca Chandler[3], Dale Nordenberg[4], Robert Chen[5]

[1]University of Washington, Seattle, USA. [2]Eduardo Mondlane University, Maputo, Mozambique. [3]Coalition for Epidemic Preparedness Innovation (CEPI), Oslo, Norway. [4]Thriive, New York, USA. [5]Brighton Collaboration, Task Force For Global Health, Decatur, USA

Introduction: Functional active safety surveillance is critical for post-authorization assessment of and decision-making for vaccines for emerging infectious diseases. Data collected via active surveillance systems, such as cohort event monitoring and pregnancy registries, can be used to support the introduction of novel vaccines. Yet, active safety surveillance systems in low- and middle-income countries (LMICs) remain inadequate.
Aim/Objective: To identify what components of active safety surveillance exist or are planned in LMICs and among vaccine developers, characterize their strengths and limitations, and determine how they might be used or adapted to monitor new vaccines.
Methods: Through the efforts of the Coalition for Epidemic Preparedness Innovations (CEPI)-funded Safety Platform for Emergency Vaccines (SPEAC) project, a systematic review of the scientific and grey literature was conducted. MEDLINE, using the PubMed interface EMBASE, was searched using subject index terms, e.g., "active safety surveillance", "vaccines", "pharmacovigilance", "LMICs". Included were articles published between 2013 and the present. Searches of unpublished studies/grey literature were conducted through Google, the World Health Organization, initiatives involved in pharmacovigilance (PV), selected donors, and LMIC national PV centers and national regulatory agencies. The protocol was registered with PROSPERO and conforms with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR), with guidance from a Steering Committee. Additionally, a cross-sectional descriptive online survey and interviews is underway with key informants to further identify current and planned active safety surveillance activities. A narrative synthesis of findings is reported, and key features of studies are compared and categorized by geography, type of medical product, disease/condition, funding source, health system and project.
Results: A total of 4,072 records were identified in our literature search after de-duplication. These records were imported into Covidence for title and abstract screening which is presently underway and then proceeding to full text review and data abstraction. Findings are reported according to relevant characteristics, including geography, methodology, vaccine(s) and/or drug(s) studied, and active surveillance system components. Strengths, weaknesses, ability to add new interventions and combine data with other systems, and the quality of the existing resources will be discussed as part of the findings.
Conclusion: Findings identify the most urgent priorities for strengthening active safety surveillance systems in a manner that leads to sustainable peri- and post-licensure vaccine active safety surveillance for LMICs and more informed safety units among vaccine developers.
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Exploring Drug Knowledge Base Usage in Medical Education: Perspectives and Practices Among Medical Students

Hager Saleh

Department of Global Public Health, Health Systems and Policy, Karolinska Institutet, Stockholm, Sweden

Introduction: Background: Knowledge bases for drug information, such as Janusmed in Sweden, UpToDate[R], ClinicalKey[R], and Drugs.com, are repositories of structured data derived from scientific

literature. These platforms, including resources like drug-drug interactions, pregnancy, and breastfeeding, provide easily accessible and evidence-based drug information. Medical students who want to be doctors must be able to access, search, navigate, and evaluate relevant information resources efficiently. Studying how medical students interact with such tools can give instructors with significant information for improving the learning experience.

Aim/Objective: Aim: The scoping review was considered to explore the available publications regarding medical students' perspectives on drug knowledge bases and how knowledge bases are integrated into their medical education. The literature search was performed in March and April 2021.

Methods: Methods: The following databases (Google Scholars, PubMed, CINAHL, and Web of Science) were considered to identify relevant publications related to drug knowledge bases and medical students between the year 2000 to 2021.

Search criteria: Journal articles in the English language, Time range: from the year 2000 to the year 2021. Keywords: (((Drug OR substance) AND ("Knowledge base*" OR Knowledgebase*)) OR "online drug information" OR "electronic drug information resources") AND "medical students" AND ("medical education" OR "pharmacological training" OR "medical training" OR "medical school").

Results: Results: A scoping review of the literature yielded 155 articles, 15 of which met the inclusion criteria. It was identified from the literature that PubMed was the Preferred. Knowledge base: the library staff was the students' primary source to know about knowledge bases, and they used their mobile devices to access medical information.

Conclusion: Conclusion: The study identifies UpToDate as the top choice among electronic resources for medical students, followed by platforms like Micromedex and Epocrates. Students prefer user-friendly web platforms like Google and Medscape. Information sources include library staff and peers, with many medical residents lacking formal drug information training. Common information needs include drug interactions and adverse effects. Canadian students heavily use mobile devices to access medical information, and Australians prefer medication apps. Barriers to usage drug Knowledge bases include a lack of skills, time constraints, and access fees.

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A Systematic Review of Pharmacovigilance System in Africa: Performance, Challenges, and Option to Enhance Pharmacovigilance

Seun Onasanya

University of KwaZulu-Natal, Durban, South Africa. Memorial University of Newfoundland, ST.JOHN'S, Canada

Introduction: Africa has made significant advancements in the realm of pharmacovigilance; presently, 50 of the 54 countries in the continent are participants in the WHO Program for International Drug Monitoring (PIDM). However, enduring issues like lax regulations, scarce resources, and inconsistent regulations affects PV systems in Africa.

This systematic review attempts to synthesize current studies assessing the performance of PV systems in African countries in the context of maturity level of PV activities among these nations, future challenges, and options to enhance PV activities in Africa.

Aim/Objective: This research provides systematic review of studies evaluating PV activities in Africa, provided challenges been faced and propose options for enhancing PV activities.

Methods: The relevant literature published from 2018 to the present was found by an electronic database search conducted in February 2024 on PubMed, Embase, Medline, and Web of Science. The included studies' reference lists were scrutinized. Hawker et al.'s nine-item checklist was used to evaluate the quality of the included studies, and the WHO PV indicators checklist was used to retrieve data. Each combination of indicators received a score, which was then used to compare the PV performance among the fifty countries.

Results: Twenty-eight different research investigations were carried out in fifty other nations, and the indicators received a total score of 36. Studies received a medium or high rating. Nine studies were rated as medium (n = 9) and nine as high (n = 19). The studies' average score on the WHO PV indicators was 19.4 out of 63 possible points. In all 50 countries, PV system performance was low (18.82/63; range: 0–28). The mean values of the "Complementary" (6.58/36) and "Core" (12.14/27) indicators. Overall, the "Structural" indicators outperformed the "Process" and "Outcome" indicators

Conclusion: The many obstacles preventing optimal PV system performance in Africa were made clear by this assessment of research that evaluate PV performance in African continent.

In order to successfully navigate the changing pharmacovigilance landscape, Africa will undoubtedly need to combine cutting-edge technologies like artificial intelligence with well-coordinated efforts and creative solutions so that the continent can set the stage for effective and comprehensive drug safety monitoring, safeguarding the welfare of its people.

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Genome-Wide Association Study on Possible Association Between Inflammatory Neuropathies and SARS-CoV2 Vaccines

Ilma Bertulyte[1], Marco Cavalli[1,2], Niclas Eriksson[1,3], Dag Nyholm[1], M Gabriella Scordo[1], Mia Wadelius[1], Pär Hallberg[1]

[1]*Department of Medical Sciences, Uppsala University, Uppsala, Sweden.* [2]*Department of Immunology, Genetics & Pathology, Uppsala University, Uppsala, Sweden.* [3]*Uppsala Clinical Research Center, Uppsala, Sweden*

Introduction: SARS-CoV2 vaccines have emerged as a powerful weapon against the COVID-19 pandemic, but questions about their safety have arisen. Rare inflammatory neuropathies, including Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), have been suggested to be associated with SARS-CoV2 vaccines. However, establishing causality remains elusive, and the underlying pathological mechanisms remain unclear.
Aim/Objective: The aim of this study was to assess potential genetic factors contributing to the development of GBS or CIDP after SARS-CoV2 vaccination.
Methods: Cases were identified through the Swedish national database of spontaneously reported adverse drug reactions. We conducted a genome-wide association (GWAS) study in 16 individuals (mean age 63 years (range 43-82 years), male gender 70%) who developed GBS or CIDP after SARS-CoV2 vaccination and compared the results with a control cohort population of unrelated individuals from the Swedish Twin Registry (n = 4891).
Genotyping of cases was performed with the Illumina OmniExpressExome 960K or Illumina InfiniumOmniExpressExome-8v1-3_A arrays, and for controls with the Illumina HumanOmniExpress 700K array. Imputation was performed using the TOPMED reference panel.
Results: Gene set analysis of rare coding variants showed that the frequency of variants in the Adhesion G protein-coupled receptor V1 (ADGRV1) gene was higher in the GBS and CIDP group than in the controls (p-value = $2.62*10^{-6}$). GWAS analysis showed no significant results.
Adhesion G protein-coupled receptor V1 is expressed on mature oligodendrocytes and is associated with the expression of myelin-associated glycoprotein (MAG), which has inhibitory effects on the process of nerve repair. Loss of function variants in this gene are known to cause Usher syndrome characterized by retinitis pigmentosa and sensorineural hearing loss, and rare variants have been associated with epilepsy.
Conclusion: Our results suggest that rare variants in the ADGRV1 gene may be associated with developing inflammatory neuropathies after SARS-CoV2 vaccination.
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A Systematic Review of Case Reports of Allergic and Hypersensitivity ADRs Associated with PEG-Granulocyte Colony-Stimulating Factor (PEG-GCSF) and PEG-Asparaginase (PEG-ASE)

Hyuk Chang, Hyunmin You, Marie-Christine Jones, Anthony R Cox

School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom

Introduction: Despite improvements in manufacture processes, recombinant biological products often present higher risk of allergic and hypersensitivity adverse drug reactions (ADRs), due to their potential immunogenicity. PEGylation has been suggested to improve the stability, pharmacokinetics, and tolerability of such products. However, PEG has itself been implicated in hypersensitivity reactions, especially when used as an excipient for the formulation of biologicals and lipid-based nanoparticles.
Aim/Objective: The aims were two-fold: 1) to identify the type of allergic and hypersensitivity ADRs resulting from the administration of PEGylated granulocyte colony-stimulating factor (PEG-GCSF) and asparaginase (PEG-ASE) and 2) to assess the role of corticosteroids and anti-histamines in the management of these ADRs.
Methods: A systematic literature review of case reports and case series on drug-induced ADRs was undertaken between January 1992 and November 23 for PEG-ASE, and from January 2000 to November 2023 for PEG-GCSF, reflecting the period since the drugs were first approved for clinical use. Data on the type, onset and management of hypersensitivity reaction was extracted.
Results: 53 ADR cases were identified for PEG-ASE. Out of these, 9 cases related to a drug-induced allergic/hypersensitivity ADR mainly anaphylaxis or anaphylactoid-reactions. Most ADRS appeared after the 2nd or 3rd dose. However, 5 cases happened during or right after the first infusion. In all cases ADRs were managed by treatment with intravenous fluids, corticosteroids, and anti-histamines (diphenhydramine), with 3 cases requiring administration of epinephrine.
For PEG-GSCF, 60 ADR cases were identified of which 5 were hypersensitivity/allergic reactions. Two cases presented as a skin rash appearing 1- or 7-days after PEG-GCSF administration and were managed with anti-histamines and corticosteroids. Three cases reported anaphylaxis or anaphylactoid reactions which appeared within 1 hour of the first dose and required fluid replacement, epinephrine, and corticosteroids. Interestingly, one case could be switched to non-PEG GCSF without ADRs.
Conclusion: A similar number of ADR case reports were identified for both drugs over the period considered. Both PEGylated biologicals were associated with hypersensitivity/allergic reactions. Onset was varied, but early onset could suggest prior sensitisation to any component of the formulation, including PEG, a widely used pharmaceutical excipient also present in many personal care products. In the UK, premedication with anti-histamines and corticosteroids is recommended for PEG-ASE, but not PEG-GCSF. Further studies could determine if this recommendation should be expanded and whether patients should be assessed for possible hypersensitivity prior to initiating treatment with PEGylated biologicals.
References

230 Unraveling Psychotic Disorders: A 10-Year Analysis of Cases Received by the Portuguese National Pharmacovigilance System

João Paulo Fernandes[1,2,3], André RTS Araújo[4,5], Márcia Silva[3], Bruno Sepodes[1,2], Carla Torre[1,2]

[1]Faculdade de Farmácia, Universidade de Lisboa, Lisbon, Portugal. [2]Laboratory of Systems Integration Pharmacology, Clinical and Regulatory Science, Research Institute for Medicines of the

University of Lisbon (iMED.ULisboa), Lisbon, Portugal. [3]INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon, Portugal. [4]Biotechnology Research, Innovation and DesiGn for HEalth ProductS (BRIDGES), Polytechnic Institute of Guarda, Guarda, Portugal. [5]LAQV, REQUIMTE, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal

Introduction: Psychotic disorders include schizophrenia, schizoaffective and schizophreniform disorder, brief psychotic disorder, and delusional disorders (1). They present positive symptoms like persistent delusions, hallucinations, disorganized thinking, and grossly disorganized behavior, as well as negative symptoms such as reduced emotions and motivation, along with changes in movement, causing major disruptions in reality perception and behavior (2). Substance or medication-induced psychotic disorders arise from various prescription medicines and illicit substances, triggering temporary psychotic symptoms (1).

Aim/Objective: To analyze and characterize cases of suspected adverse drug reactions presenting as psychotic disorders received by the Portuguese National Pharmacovigilance System.

Methods: Retrospective analysis of Individual Case Safety Reports (ICSRs) containing at least one MedDRA Preferred Term (PT) related to the High Level Group Term 'Schizophrenia and other psychotic disorders', reported to the Portuguese National Pharmacovigilance System between January 1, 2014, and December 31, 2023. Duplicates were excluded. Characterization of ICSRs considered patient demographics, reported suspected medicinal products and category of adverse drug reactions, seriousness and type of reporter.

Results: A total of 208 ICSRs were identified, with 94.2% (n = 196) being reported by healthcare professionals. Most were related to individuals aged between 18 and 64 years old (n = 153), and men (n = 131). The vast majority of cases were classified as serious (n = 185), with 39.9% (n = 83) of these being associated with or extending hospitalization. Paliperidone was the most frequently reported medicinal product, being classified as suspected in 50.5% (n = 105) of the ICSRs. Upon extending the analysis to all antipsychotics classified under the Anatomical Therapeutic Chemical (ATC) code N05A, a total of 138 cases related to at least one of these medicinal products were identified. The most frequently reported PT was 'Schizophrenia', accounting for 58.7% (n = 81) of these cases. For the remaining 70 ICSRs, 74.3% (n = 53) were associated with a single suspected medicinal product. The most frequently reported ATC groups were N06 ('Psychoanaleptics') with 10 reports, followed by H02 ('Corticosteroids for systemic use') and J05 ('Antivirals for systemic use'), each with 6 reports. The most frequently reported PT was 'Psychotic disorder', presented in 30 (42.9%) of the ICSRs.

Conclusion: The majority of reported psychotic disorder cases to the Portuguese National Pharmacovigilance System involved antipsychotic medicines, prompting inquiries into causality. Detailed reporting is essential for assessing potential confounding factors and facilitating a thorough evaluation of causality, thereby playing a crucial role in identifying new risks and safeguarding public health.

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Defective Medicines: A Retrospective Review of Cases Received by the Portuguese National Pharmacovigilance System Over the Last Ten Years

Adriana Gamboa, João Paulo Fernandes, Ana Moreira, Sandra Queiroz, Márcia Silva

INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon, Portugal

Introduction: Some irregularities in medicine quality are often only identified post-marketing. Defective medicines may exhibit various issues such as defects in the product itself, packaging materials, or other components such as patient information leaflets (1). Critical deficiencies in high-risk medicines may pose significant health hazards to patients, some of which could be life-threatening and require immediate corrective action (2).

Aim/Objective: To analyze and characterize cases related to defective medicines received by the Portuguese National Pharmacovigilance System.

Methods: Retrospective analysis of Individual Case Safety Reports (ICSRs) containing at least one MedDRA Preferred Term (PT) related to the High Level Term (HLT) 'Product Quality Issues NEC' or "Device Issues NEC', reported to the Portuguese National Pharmacovigilance System between January 1, 2014, and December 31, 2023. Duplicates and literature cases were excluded. Characterization of ICSRs considered patient demographics, reported suspected medicinal products and MedDRA PT, seriousness and type of reporter.

Results: A total of 330 ICSRs were identified, with 73.0% (n = 241) being reported by healthcare professionals. Most were related to individuals aged between 18 and 64 years old (n = 102), and women (n = 210). Around thirty percent of the cases were classified as serious (n = 96), with 25.0% (n = 24) of these being related to situations of disability or other criteria of greater seriousness. The most frequently reported medicinal products were formoterol and budesonide (Anatomical Therapeutic Chemical (ATC) code R03AK07), levonorgestrel (ATC code G02BA03), and oxygen (ATC code V03AN01), with 16, 15, and 13 cases reported, respectively. The most frequently reported PTs related to defective medicines were 'Product substitution issue' (n = 99), 'Product quality issue' (n = 68), and 'Product complaint' (n = 50), all pertaining to the HLT 'Product Quality Issues NEC'. Regarding the HLT 'Device Issues NEC' the most reported PTs were 'Device Issue' (n = 20), 'Device dislocation' (n = 16), and 'Device leakage' (n = 16). With respect to MedDRA PTs associated with physiopathological alterations, the most frequently reported in conjunction with terms related to defective medicines were 'Malaise' (n = 21), 'Nausea' (n = 20) and 'Dyspnoea' (n = 18). In around 12% of the ICSRs (n = 38), the PT 'Drug ineffective' was reported.

Conclusion: This retrospective study analyzed and characterized cases related to defective medicines received by the Portuguese National Pharmacovigilance System over a ten-year period. The findings underscore the critical role of pharmacovigilance in detecting, evaluating, and monitoring defective medicines, while regulatory authorities play a pivotal role in implementing corrective and preventive measures to ensure the safety and efficacy of medicines in the market. Together, these observations emphasize the ongoing importance of active and collaborative surveillance involving healthcare professionals, the pharmaceutical industry, regulatory authorities, and citizens to safeguard patient safety and medicine quality.

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Adverse Drug Reactions Reported by Community Pharmacists in the Last 6 Years–A Landscape Analysis

Ana-Marta Silva[1], Ana Vales[2], Francisco Silva[3], João Fernandes[4], Ana Moreira[4], Márcia Silva[4]
[1]Center for Health Technology and Services Research (CINTESIS); Faculty of Medicine of University of Porto; University Institute of Health Sciences - CESPU (IUCS-CESPU), Porto, Portugal. [2]Plena Pharmacy, Porto, Portugal. [3]University Institute of Health Sciences - CESPU (IUCS-CESPU), Porto, Portugal. [4]INFARMED - National Authority of Medicines and Health Products, I.P., Porto, Portugal

Introduction: According to the European Medicines Agency (EMA), an adverse drug reaction (ADR) is a noxious and unintended response to a medicine [1]. Community pharmacists (CP), due to their accessibility and frequent interaction with patients, are in a unique position to detect and report ADRs.

Aim/Objective: To analyze the individual case safety reports (ICSRs) made by community pharmacists to the Portuguese National Pharmacovigilance System (NPS) in the last 6 years.

Methods: Retrospective study of ICSRs made by CP, received directly to the Portuguese NPS (01/2018 to 12/2023). The analysis included the number of community pharmacists' ICSRs for each year of participation in the Portuguese NPS and the seriousness criteria. The main groups of suspected drugs (Anatomical Therapeutic Chemical - ATC group) and the main groups of organ systems (SOC - MedDRA coding) affected by ADRs were identified. The ADR was also analyzed to determine whether or not it was listed in the SmPC at the reporting date. A descriptive analysis of the patient's demographic data (age group and gender) was carried out.

Results: Over six years, the Portuguese NPS collected 34722 ICSRs, of which 2069 (5.9%) were carried out by CP. The percentage of ICSRs grew until 2020 (8.4% of total ICSRs), with a drop in 2021 (1.8%). In 2023, the rate of ICSRs increased again (13.7%). The most reported cases were serious (57.6%), and the most frequently mentioned seriousness criteria were: "clinically important" (73.6%), "disability" (16.4%), and "hospitalization" (7.2%). Regarding the analysis of the medications involved in the ATC group, group J was the most frequently reported (32.4%), followed by groups N (19.0%) and C (15.4%). Regarding ADRs (SOC hierarchical level), the three most reported ADR groups were "General disorders and administration site conditions" (19.8%), "Gastrointestinal disorders" (16.8%), and "Nervous system disorders" (14.5%). Regarding the description of ADRs in the SmPC, 23.9% were not listed. Regarding patient demographics, the median age is 63 years [IQR 25%: 46; IQR 75%: 73], with women being the population group with the most reported ICSRs (70.7%).

Conclusion: The analysis of ICSRs by CP reinforces the vital role of these professionals in monitoring the safety profile of marketed medicines. Evidence shows that there was global awareness regarding the administration of vaccines against COVID-19 in CP, with great concern about reporting ADR. It should also be noted that CP reports serious ADRs and, in some cases, are not listed in SmPC, demonstrating that their participation is beneficial. Other studies [2, 3] carried out in this professional group mention similar data on the group of most reported medications, as well as the organ system most affected by ADR. The national data collected may also enable the identification of benchmarks that drive the evolution of the NPC, promoting the increasing participation of these professionals.

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ADR Reports in Portugal: Healthcare Professionals vs Consumers - 10 Years of Experience

Ana-Marta Silva[1], Inês Ribeiro-Vaz[2], Joana Marques[3], Jorge Polónia[2]
[1]Center for Health Technology and Services Research (CINTESIS); Faculty of Medicine of University of Porto; University Institute of Health Sciences - CESPU (IUCS-CESPU), PORTO, Portugal. [2]Northern Pharmacovigilance Centre; Center for Health Technology and Services Research (CINTESIS); Faculty of Medicine of University of Porto, Porto, Portugal. [3]Center for Health Technology and Services Research (CINTESIS); Nursing School of Porto, Porto, Portugal

Introduction: From 07/2012, with the transposition into national legislation of Directive No. 2010/84/EU of the European Parliament and of the Council, consumers, not healthcare professionals, can report suspected adverse drug reactions (ADR).[1]

Aim/Objective: The objective is to characterize the national ADR report made by consumers since their entry into the National Pharmacovigilance System (NPS) and compare it with health professionals' (HCP) reports.

Methods: Retrospective study of ADR reports received directly at the NPS (excluding industry reports and clinical trials) between 01/2013 and 12/2022. The analysis included totals for each year of NPS participation, as well as seriousness and seriousness criteria. The main groups of suspected medicines (Anatomical Therapeutic Chemical - ATC group) and the types of ADR (SOC hierarchical degree of MedDRA coding) were determined. A descriptive analysis of the patient's demographic data (age group and gender) was carried out.

Results: Over 10 years, the NPS collected 46855 reports, of which 8104 (17%) came from consumers. The number of consumer reports increased significantly in 2021. Regarding the seriousness of reports, there was a similar proportion as a whole in the case of HCP (54%) compared to consumer (55%) reports. The seriousness criteria most frequently chosen in consumer reports were the following: "clinically important" (47%) and "disability" (45%), while in HCP reports, it was "clinically relevant" (66%) and "hospitalization" (15%). Regarding the analysis of the medicines involved, when comparing the 5 most reported ATC groups, it appears that 4 were common to consumers and HCP reports (ATC Groups: C, J, M, and N), although in different proportions. Regarding ADR (SOC hierarchical level), the 5 most reported ADR groups are the same in reporters, consumers, and HCP groups. Regarding the ADR description in the Summary of Medicinal Product Characteristics (SmPC), we found the proportion of reports containing at least one undescribed ADR was higher in the consumer group (46%) than in the HCP (25%). Regarding patient demographic data, consumer and HCP reports were very similar; most reports are from female patients between 18 and 64 years old.

Conclusion: Overall, evidence shows that consumer reporting is increasing. The information resulting from consumer reports is relevant in contributing new information, reporting ADR not yet described in the SmPC, and about the report's seriousness, as they

specify more clearly how the ADR affected the quality of the patient's life. In this sense, consumer participation adds value to health. The national data collected may also enable the identification of benchmarks that contribute to leveraging the improvement of the NPS with increasing citizen participation. ADR resulting from vaccination against COVID-19 demonstrated that the report is accessible by HCP and consumers. Therefore, taking advantage of this global awareness is essential to create an engagement among all NPS stakeholders, mainly to involve citizens increasingly.

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Visits to Healthcare Units to Raise Awareness and Improve Implementation of Additional Risk Minimization Measures (aRMMs) in Saudi Healthcare Settings

Atheer Aldayel, Maram Aljebreen, Amal Alshatri, Naser Al Jaser, Fawaz Al-Harbi

Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Introduction: *The dissemination and implementation of aRMMs are crucial for enhancing medication safety.[1] The Saudi Food and Drug Authority (SFDA), in collaboration with Regional Pharmacovigilance officers (RPVOs), initiated a project targeting healthcare providers (HCPs) across various governmental and private hospitals.*

Aim/Objective: *The project aimed to increase awareness and understanding of aRMMs, improve their implementation, promote adverse drug event reporting, and build communication channels with HCPs through educational visits.*

Methods: *The study employed a mixed-method approach, including pre- and post-educational visit surveys and discussions to evaluate HCPs recipients, knowledge, and implementation of aRMMs. 28 RPVOs were trained in 2023 by SFDA to undertake the visits. HCPs completed the pre-visit surveys before the commencement of the sessions and the post-visit surveys immediately after. Knowledge was scored out of 5 and compared pre- and post-visit using Wilcoxon signed rank tests.*

Results: *RPVOs conducted 100 visits to the HCPs in 2023. Pre-surveys were filled by all HCPs (100); however, only 79 responded to the post-surveys. Most HCPs were from pharmaceutical care (n = 65), female and Saudi nationals (n = 56 and n = 80, respectively) with 5-10 years of experience (n = 35). Before visits, awareness of aRMMs was low, with only 36% having heard of them and 35% completely unaware. Few had visited the SFDA website for aRMMs (18%) or attended a lecture (17%). Though most prescribed/dispensed the relevant medications (78%), only 43% knew they required aRMMs and 9% provided patients with the materials. After visits, 78 (98.7%) knew where to find approved aRMMs. Self-rated knowledge improved, with 54 (68.4%) rating understanding as greatly improved versus 20 (25.3%) rating it adequate beforehand. Knowledge scores significantly increased between pre- and post-survey ($P < 0.001$). The median score increased from 4 (IQR: 3.5) to 5 (IQR: 4.5). Knowledge scores improved for 38 (48%) of participants, decreased for 6 (8%), and did not change for 35 (44%). Most HCPs found the aRMMs materials very useful, with 48 (60.8%) rating them as such. Additionally, 40 (50.6%) were highly satisfied with the visits. 73 (92.4%) were willing to accept future visits about aRMMs.*

Conclusion: *The educational visits conducted by RPVOs significantly improved HCPs' knowledge and understanding of aRMMs. While the project made progress, it also identified areas for further improvements. Increasing the frequency of visits, using various educational and awareness methods, and integrating aRMMs into clinical systems can enhance the impact of this initiative. The findings support expanding such initiatives to ensure consistent aRMMs application in healthcare settings.*

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The Crucial Role of Teratovigilance in Assessing Medication Risks During Pregnancy

Afaf BOUQOUFI, Fatima AIT EL HADJ, Youssef KHABBAL

Faculty of Medicine and Pharmacy Ibn Zohr University, Agadir, Morocco

Introduction: The use of medications during pregnancy is becoming a source of concern for expectant mothers, as well as for the healthcare professionals consulted (1). Several factors intervene and increase the risk of fetal drug exposure (2). Teratovigilance, which falls under the National Pharmacovigilance System, intervenes to ensure continuous monitoring of the health impact of healthcare product use during pregnancy(3).

Aim/Objective: To determine the role of teratovigilance in assessing the risks of medications in pregnant women.To determine the role of teratovigilance in assessing the risks of medications in pregnant women.

Methods: A bibliographic search on databases was conducted using the following keywords: Drug risk, adverse effects, teratogenicity, teratovigilance, medication, and pregnancy.

Results: Teratovigilance activities involve monitoring and analyzing reports of adverse events and outcomes in pregnant women exposed to medications. By identifying patterns and trends in reported cases, teratovigilance helps assess the potential risks associated with specific medications or classes of drugs during pregnancy. Teratovigilance plays a crucial role in enhancing patient safety. It helps healthcare providers and pregnant women make informed decisions about medication use, weighing the potential benefits against the risks to both the mother and the fetus. Epidemiological studies are generally designed to determine the association between the occurrence of malformations and drug intake (cohort studies). These studies are rare because their duration and costs are higher. Databases such as Vigibaze and Vigiflow are used by regulatory agencies to inform regulatory decision-making processes, such as drug approval, labeling changes, and risk management strategies. These data help regulatory authorities assess the safety profile of medications and take appropriate regulatory actions to protect public health.

Conclusion: Teratovigilance offers the possibility of generating a signal or an alert and provides information on exposure to healthcare products as part of a retrospective exposure assessment, chronic exposure to treatment (preventive assessment), and in the context of future exposure (prospective evaluation).

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Risk Communication about Medications: Initiatives for Improvement in Saudi Arabia

Najd Alabdulrahman, Aljawharah Albabtain, Nada AlOwedi, Naser Al Jaser, Fawaz Al-Harbi

Saudi Food & Drug Authority, Riyadh, Saudi Arabia

Introduction: The purpose of communicating drug safety information to healthcare providers (HCPs), patients, and the public is to ensure the safe and effective use of post-marketed medications, which is one of the responsibilities of the Saudi Food and Drug Authority (SFDA).
Aim/Objective: To share the Drug Safety and Risk Management Directorate Department (DSRM) initiatives for improving risk communication about medicines. To share the Drug Safety and Risk Management Directorate Department (DSRM) initiatives for improving risk communication about medicines.
Methods: We included all initiatives targeted HCPs and patients that were performed in 2023 to improve risk communication about medicines such as: scientific activities, short messages, visits to Healthcare Units, awareness campaign, animated videos and focus group.
Results: In 2023, DSRM at SFDA performed numerous activities directed to HCPs and the public such as:

- Adding 214 risk minimization measures to Tamni application in the form of Alert Messages in both languages "Arabic & English"
- Conducting a campaign in private hospitals to raise awareness about Risk Minimization Measures for Medications
- Conducting a workshop to improve implementation and distribution of risk minimization measures on the National level
- Producing 42 educational materials in the form of infographics
- Conducting 23 scientific lectures directed to HCPs to increase health practitioners' awareness of risk minimization measures
- Performing 100 visits to Healthcare Units and conducting focus group meetings with HCPs and patients to have feedback on six approved Additional Risk Minimization Measures for medicinal products

Conclusion: The DSRM at SFDA uses different tools to improve medicines risk communication in Saudi Arabia. A constant exchange of information and communication between regulatory authorities and its stakeholders such as pharmaceutical companies, HCP, public and health sectors should be maintained and improved to ensure proper delivery of medicines risk communication to the target audience. The DSRM at SFDA uses different tools to improve medicines risk communication in Saudi Arabia. A constant exchange of information and communication between regulatory authorities and its stakeholders such as pharmaceutical companies, HCP, public and health sectors should be maintained and improved to ensure proper delivery of medicines risk communication to the target audience.
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Teratogenic Effect of Medicinal Plants Used During Pregnancy by Pregnant Women from EMRO's Region: A Systematic Review

Afaf BOUQOUFI[1], Laila LAHLOU[1], fatima Ait El hADJ[1], Mohamed Abdessadek[2], Majdoline Obtel[3], Youssef KHABBAL[1]

[1]Faculty of Medicine and Pharmacy Ibn Zohr University,, Agadir, Morocco. [2]Higher School of Technology, Ibn Zohr University, Laayoune, Morocco. [3]4Laboratory of Social Medicine (Public Health, Hygiene and Preventive Medicine), Department of Public Health, Faculty of Medicine and Pharmacy, University Mohammed, Rabat, Morocco

Introduction: In the world population, access to medication remains a major public health problem that forces pregnant women to self-medicate with several sources such as medicinal plants. Medicinal plants and herbal remedies contain substances that can be toxic to the fetus. Potential effects of use of medicinal plants are embryotoxicity, teratogenic, and abortifacient effects.
Aim/Objective: This work was to provide a systematic literature review of available data on medicinal herbs use during pregnancy in the EMRO region and risk assessment of plants used according to the literature.
This work was to provide a systematic literature review of available data on medicinal herbs use during pregnancy in the EMRO region and risk assessment of plants used according to the literature.
Methods: The finding data was obtained using PubMed, Scopus, and Web of Science databases from January 2011 to July 2021.The survey was carried out with Boolean operators and using (MeSH) terms. We used Rayyan website for abstracts and titles screening. These were followed by reading the full texts to identify the final studies to be included . The data extracted covered the country of studies, year of publication, prevalence of herbal medicine use, details of herbal medicines used, characteristics of users, maternal conditions treated by herbal medicines and reasons of use.
Results: Overall, twenty-nine studies included in this review. The prevalence varied from 19.2% to 90.2%. A total of 65 different medicinal plants species used in traditional treatment of gestational health ailments/symptom complexes throughout EMRO's region. The most commonly used herbs identified were: ginger, thyme, peppermint, sage, chamomile, fenugreek, black seeds, cinnamon and cumin. Most of these plants are contraindicated during pregnancy due to their pharmacological activity or the structure of their constituents causing teratogenic risks for the fetus.
Conclusion: The use of herbal medicines among pregnant women is prevalent. Given the scarcity of studies, it is recommended that future studies should focus on safety and effects of herbal medicines on pregnancy outcome.
The use of herbal medicines among pregnant women is prevalent. Given the scarcity of studies, it is recommended that future studies should focus on safety and effects of herbal medicines on pregnancy outcome.
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Drug Safety During Pregnancy: The Big Challenge of Maternal and Neonatal Health

Afaf BOUQOUFI, Fatima Ait el hadj, Youssef KHabbal

Faculty of Medicine and Pharmacy Ibn Zohr University, Agadir, Morocco

Introduction: Drug safety in pregnancy is very important. Data on drug risks in pregnancy are scarce since the thalidomide scandal 60 years ago. Nevertheless, individualized risk information is

indispensable for clinical decision-making. Often, there is uncertainty about how to interpret the available scientific data, and for the majority of drugs, clinical experience is still insufficient with respect to their safety in pregnancy.

Aim/Objective: To conduct a literature review about drug safety during pregnancy

Methods: We searched PubMed and the available literature on the antiepileptic drugs exposure during pregnancy with the following search terms: "pregnan*", "obstetric*" and combined with "Drugs*", "drugs safety" and "teratogenic", "adverse effect".

Results: Medicines taken during pregnancy can potentially affect the normal course of pregnancy and impact embryonic and fetal development. Systematic testing of the teratogenic properties of drugs in humans is not possible, the epidemiological approaches for risk evaluation are of major importance. There are several possibilities to assess the safety of drugs in pregnancy once they have been marketed. Observational data are the most important such data are collected through the risk consultation process. Prospective cohort studies which have a number of methodological advantages compared with other study types allow for estimating relative risks for birth defects, pregnancy loss, and other developmental anomalies. The adverse developmental effects of pharmaceutical products may include not only congenital malformations but also growth restriction, fetal death, and functional defects.

Conclusion: Medication in pregnancy counseling requires risk characterization according to individual clinical circumstances. Treatment selection recommendations individual risk assessment after exposure, and causality assessment in congenital anomalies. Medication in pregnancy counseling requires risk characterization according to individual clinical circumstances. Treatment selection recommendations individual risk assessment after exposure, and causality assessment in congenital anomalies.

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Pharmacovigilance and Onco-Cardiology: A Synergistic Interaction

Agnès Lillo[1], Imen Hamdi[2], Soledad Henriquez[2], Raphael Colle[2], Djidjiga MANSOURI[2], Francesco Cribari[2], Pierre Charles[2], Christine Le Beller[1], Christophe Caussin[2], Mariana Mirabel[2]

[1]HEGP - Assitance Publique Hopitaux de Paris, Paris, France. [2]Institut Mutualiste Montsouris, Paris, France

Introduction: Nowadays, cardio-oncology is a major discipline. On one hand, the therapeutic arsenal has exploded, with major advances such as immune checkpoint inhibitors (ICIs), and tyrosine kinase inhibitors. On the other hand, the incidence of cancer is growing, and patients with several comorbidities, including aged patients, need aggressive therapy. The cardio-oncology goal is threefold: to ensure, for patients with cardiovascular disease, the best cancer treatment, to anticipate as possible the cardiotoxicity of cancer therapy, and if a cardiac event occurs, the treatment of the patient, the assessment of the drug causality, and the discussion of the outcome of the cancer therapy.

Aim/Objective: To present cardio-oncology activity from a pharmacovigilance perspective

Methods: A single center, retrospective analysis of patient's cases discussed in the weekly meeting of an onco-cardiology unit. Patients were referred for cardiac symptoms: therefore, both a complete cardiovascular evaluation (clinical exam, blood tests, ECG, transthoracic echocardiogram, cardiac magnetic resonance imaging) and a clinical evaluation by the internal medicine team were performed and their cases were discussed in a weekly basis.a single center, retrospective analysis of patient's cases discussed in the weekly meeting of an onco-cardiology unit. Patients were referred for cardiac symptoms: therefore, both a complete cardiovascular evaluation (clinical exam, blood tests, ECG, transthoracic echocardiogram, cardiac magnetic resonance imaging) and a clinical evaluation by the internal medicine team were performed and their cases were discussed in a weekly basis.

Results: In 2022 and 2023, the cardiology unit held 100 weekly meetings. During these meetings, the cases of 714 patients were discussed. After analysis, 182 cases of cardiovascular adverse drug reactions (ADRs) were recorded in the French pharmacovigilance database (25% of the cases discussed), and 9 additional cases of non-cardiac ADRs were recorded. Most of the patients were women (79 %), the median age was 58 (17-95) years old; the female prevalence is explained by the close collaboration with a centre dedicated to breast cancer (35% of the ADRs).

The cardiac ADRs, by decreasing number and with the main drugs involved were: heart failure and left ventricular dysfunction (72 cases) mainly with anthracyclines; myocarditis (56 cases) with ICIs; ischemic heart disease (25 cases) mainly related to fluorouracil (8 cases), isolated troponin elevation (14 cases) with ICIPs; cardiac arrhythmias (7 cases) mainly with bruton tyrosine kinase inhibitors and 8 miscellaneous ADRs (2 pericarditis, one QT prolongation). Cancer therapy was continued in the majority of cases (62% of the cases), and in 17% of cases the possible re-introduction (under surveillance) of the involved drug was authorized.

Conclusion: The collaboration with a cardio-oncology unit is a major opportunity for pharmacovigilance practitioners to be associated to patient's care and to improve their knowledge of cardiac ADRs in daily practice.

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The Use of Mobile Application Versus Other Reporting Channels for Adverse Events Reporting During COVID-19 Vaccine Deployment in Ghana

Jeremiah Ewudzie-Sampson[1], Frances Baaba da-costa Vroom[2], Delese Mimi Darko[1], Seth Seaneke[1], George Tsey Sabblah[1], Margret Gyapong[3]

[1]Food and Drugs Authority, Accra, Ghana. [2]University og Ghana, Accra, Ghana. [3]University of Health and Allied Sciences, Ho, Ghana

Introduction: Tools available for reporting adverse events following immunization (AEFIs) include paper forms, telephone calls, web-based reporting and text messages (Laryea et. al,. 2022). In recent times, some researchers have focused on the use of modern communication technologies such as mobile phone applications as an

effective tool to increase reporting of adverse reactions and improve the communication of new drug/ vaccine safety information (de Vries et al., 2018).

Aim/Objective: To compare the use of the Med Safety App for reporting of adverse reactions vis-à-vis other reporting tools during the deployment of COVID-19 vaccination as well assessing the awareness of the use of the Med Safety App for reporting AEFIs among healthcare professionals.

Methods: The study was a retrospective and cross-sectional quantitative study using both primary and secondary data; a quantitative descriptive analysis was done on 4,389 spontaneous AEFIs reports from COVID-19 vaccines deployed in Ghana from March 2021 to December 2022. A 30-item novel self-administered questionnaire was administered to 147 participants made up of public health nurses, disease control officers and general nurses/ midwives within the Ga West Municipal and Tema Metropolitan Assemblies.

Results: Comparatively, 68.2% (114) AEFIs received through the App were reported within 0-3 days compared to 67.3%, 57.4% and 3.1% for SafetyWatch System (web-based), telephone calls and AEFI paper reporting form respectively. Majority of the healthcare professionals (128, 87%) had not heard of the Med Safety App; however, 28.08% of participants preferred the use of the App for reporting AEFI compared to paper AEFI forms (29.45%) and telephone (30.82%).

Conclusion: The App was found to be very useful in terms of timeliness of identification of AEFIs, however, there was low awareness of the use of the App among healthcare professionals in Ghana.

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A Decade of Implementation Good Pharmacovigilance Practice in Lower Middle-Income Country: A Case Study from Ghana

Delese Darko, Seth Seaneke, Edwin Nkansah, George Tsey Sabblah, Adela Ashie, Abena Asamoa-Amoakohene, Iverta Naa Dedei Addi, Thomas Nettey, Memuna Alimin Maiga

Food and Drugs Authority, Accra, Ghana

Introduction: Legal mandate for national medicine regulatory authorities (NMRAs) to effectively carry out vigilance activities is critical in ensuring patient safety. The Ghana Food and Drugs Authority (FDA) was established in August 1997 under the Food and Drugs Act, 1992 (PNDCL 305B)[1]. The Act made provision for healthcare professionals to report adverse reactions to regulated medicinal products with no clear requirements for marketing authorization holders (MAHs) to be responsible for safety of marketed products. In 2012, the Public Health Act (PHA), Act 851 was enacted with specific sections for MAHs to designate local representative with oversight of safety monitoring of marketed products[2].

Aim/Objective: To assess the impact of the PHA 2012, Act 851, Section 125 on compliance by MAHs to good pharmacovigilance practice principles and contribution to patient safety.

Methods: A descriptive analysis was carried out on existing data to identify trends of number of qualified persons for pharmacovigilance, Good Pharmacovigilance Practice (GPvP) inspections conducted, number of Periodic Safety Update Reports (PSURs), Risk Management Plans (RMPs), safety variations and individual case safety reports (ICSRs) submitted by the MAH's since 2012 to 2023.

Results: The finding of the analysis are:

1. 209 QPPV's trained in collaboration with the Africa Collaborating Centre for Pharmacovigilance (ACC) from May 2015 to October 2023.
2. 98 GPvP inspections conducted between 2016 and 2023.
3. 207 PSURs and 94 RMPs submitted from 2018 to 2023.
4. 312 label variations received between 2021 to 2023.
5. 1,018 ICSR received from 2014 to 2023.

Enablers for effective implementation of the legal mandate.

1. Development of formal training for QPPVs which provided them with basic knowledge and skills to undertake their role
2. Engagement of MAH managers and CEOs to obtain buy-in prior to implementation to ensure understanding of QPPV requirements for maximum support to be provided to QPPVs.
3. Annual QPPV forum to identify solutions to implementation problems being faced.
4. Provision of guidance documents and templates to assist work of QPPV.

Challenges:

1. Request to reschedule GPvP inspections due to unavailability of QPPVs sometimes due to frequent resignations.
2. Delay in submission of corrective and preventive action plan.
3. Submitting safety variations in the wrong format therefore delaying review.
4. QPPVs have other roles potentially affecting time dedicated to QPPV role.

Conclusion: The implementation of the Public Health Act 2012, Act 851 has significantly strengthened pharmacovigilance systems within pharmaceutical companies leading to improved medication safety standards. This has instilled confidence in both healthcare professionals and consumers regarding the safety and efficacy of marketed drugs in Ghana.

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A Guide for the Correct Management of High-Risk Drugs as a Tool for Integrated Key Stakeholders in Colombia

Patricia Zuluaga[1], Angela Caro[2], Juan Pablo Botero[3], Juan Pablo Osorio[4], Daniela Daza[1]

[1]Colombian Pharmacovigilance Association, Bogotá, Colombia. [2]Pharmacy Career Director at Pontifical Xaverian University, Bogotá, Colombia. [3]President of Hospital Pharmacist´s Association, Bogotá, Colombia. [4]Hospital Pharmacist´s Association, Bogotá, Colombia

Introduction: The cycle of use of medicines, since their production by a market authorization holder (MAH) included the use by the patient, could be interrupted due to different human and process factors, producing medication errors. Considering the death of two children in Bogotá, Colombia during 2020, there is a latent need to develop strategies and tools to help in the mitigation of medication errors included those produced by high-risk medicines, and a call to action for all the stakeholders (hospitals, MAH, HCP, academy, government) involved in the process

Aim/Objective: To create a guide which integrates different key stakeholders´ responsibilities and actions to be taken to improve the correct management of high-risk medicines in the country.

Methods: The Colombian Pharmacovigilance Association (ACFV) made an analysis that included all the critical steps during the use of medicines that could result in a medication error. After this review

ACFV proposed to the Ministry of health some specific actions for mitigate adverse events in the future. One action point was to develop a guide for best practices in high-risk medication management.

Results: A consensus took place in Colombia lead by ACFV, with the participation of stakeholders as the Hospital Pharmacist´s Association (ACQFH) and the Ministry of Health during two years of sessions (2021- 2022). The aim was to develop the "Guide for the correct and safe management of high-risk medicines". The final guide summarizes in five sections, the recommendations for Ministry of health and other health authorities, MAH, healthcare institutions, wholesalers, health care providers, HCP and patients. The relevant topics covered provides a framework of recommendations including the importance of a list of high-risk drugs into health settings and other stakeholders, the impact of a highlight labelling, communication and education to HCP and patients, pharmacovigilance actions with high-risk medicines, prescription considerations, correct storage and other recommendations for each stage of the cycle of medicines. Finally, the information compiled in the guideline pretends define a high-level framework for a correct management of this group of medicines based in the expertise and literature available and represent an effort of articulate prevention strategies that include all the stakeholders involved.

Conclusion: The guide is an effort to identify the critical points and the stakeholders involved in the occurrence of medication errors and proposes practical actions that could be implemented at all levels to the prevention of harms associated with high-risk medicines.

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A Deep Dive into the National Pharmacovigilance Data: Analysis of Adverse Drug Reactions Reported to Contraceptive Use

Delese Darko, Seth Seaneke, Edwin Nkansah, George Tsey Sabblah, Alexander Mwinteru Derizie, Maame Serwah Koranteng, Peggy Opoku Boateng, Adela Ashie, Abena Asamoa-Amoakohene

Food and Drugs Authority, Accra, Ghana

Introduction: Reports from the World Health Organization suggest that maternal mortality is unacceptably high with 95% of maternal deaths in 2020 from low and lower middle-income countries[1] including Ghana. In 2017, 53% of pregnancies in Ghana were unintended with 23% leading to abortions[2] of which 71% were illegal thus potentially unsafe[3]. This could be prevented with contraceptives use. Africa has the lowest utilization of contraceptives[4]. Numerous studies conducted suggest misconception surrounding adverse effects of contraceptives influence Ghanaian women's decision on birth control[4,5,6,7].

In Ghana the designated telephone number of the national pharmacovigilance centre is printed at the back of family planning cards.

Aim/Objective: To analyse adverse drug reactions (ADRs) to contraceptives in SafetyWatch System (SWS), the Food and Drug Authority, Ghana (FDA) national safety database.

Methods: A descriptive study was conducted on data retrieved from SWS from 1st February 2010 to 1st February 2024. The search was conducted by active ingredients listed under the contraceptive section in the 23rd List of the WHO Model List of Essential Medicines. Results on the three main active ingredients reported were analysed by source of report (patient or healthcare professional), year report received, system organ classification (SOC) and seriousness of adverse drug reaction (ADR).

Results: A total of 138 ADRs to depo medroxyprogesterone, etonogestrel implant and levonogesterel implant were obtained. All ADRs reported were listed in the package insert. A higher number of reports 89(64.5%) in the SWS were patient reports received through telephone calls compared to higher reports by healthcare professionals 1,3254(65.7%) in VigiBase, the WHO global safety database.

The year 2019 had highest number of reports 36(26.09%) in SWS. There were 2 serious ADRs to levonogestrel and 1 to medroxyprogesterone. Most of the ADRs were under the SOCs: Reproductive system and breast disorders 45(36.9%), Vascular disorders 21(17.2%) and General disorders and administration site conditions 17(13.93%). This was similar to reports in VigiBase except that the SOC Injury, poisoning and procedural complications was in the top 3 instead of Vascular disorders.

Conclusion: There was higher number of patient reports to contraceptive use compared to healthcare professional reports. The national pharmacovigilance centre's contact number on the family planning card could have facilitated direct patient reporting to the FDA as patients could speak to a staff and have their concerns addressed or guidance given in real time. This calls for efforts to promote direct patient reporting. The few serious ADR reported suggest contraceptives used in Ghana were safe. More education should be carried out on the safety of contraceptives to increase uptake to reduce unsafe abortions and maternal mortality.

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Haemovigilance in a Low- and Middle-Income Country; Ghana's Experience

Delese A. Darko[1], Seth Seaneke[1], Edwin Nkansah[1], George T. Sabblah[1], Abena Asamoa-Amoakohene[1], Adela Ashie[1], Felicia Dwamena[1], Akosua S. Okyere[1], Shirley Owusu-Ofori[2], Dilys Padi[2], Emmanuel N. Dei[2], Mavis Okyere[2]

[1]Food and Drugs Authority, Accra, Ghana. [2]National Blood Service, Accra, Ghana

Introduction: Haemovigilance (HV), the set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through to their provision and transfusion to patients including their follow-up is essential

for safeguarding patient well-being and optimizing healthcare quality (1,2). Nevertheless, implementation in lower-middle-income countries (LMICs) poses unique difficulties.

Aim/Objective: This paper highlights Ghana's efforts in establishing a haemovigilance system, providing insights into the strategies, achievements, lessons learnt and challenges faced.

Methods: The paper provides uses institutional data, reports and academic literature to provide a comprehensive overview of the development of Ghana's haemovigilance system. It covers stakeholder engagement, capacity building efforts, review of regulations and the outcome.

Results: Strategies

- **Multi-Stakeholder Collaboration:** Actively involving all relevant governmental bodies (Ministry of Health), regulatory agencies [Food and Drugs Authority (FDA), National Blood Service (NBS)], healthcare providers, blood banks with support from an international organization Paul Ehrlich Institut (PEI) to build a comprehensive network for haemovigilance.
- **Regulatory Framework Enhancement:** Reinforcement of regulatory frameworks dedicated to haemovigilance, highlighting reporting requirements, detailing investigation procedures, and measures for quality assurance.

Achievements

- Development of regulatory documents
  - Haemovigilance framework and Guidelines on Haemovigilance in Ghana
- Development of training materials for healthcare providers involved in the blood transfusion chain

Lessons learnt

- Use of existing pharmacovigilance system to improve the haemovigilance system taking into account Ghana's healthcare infrastructure and regulatory environment.
- The need to secure long-term funding and institutional support for the haemovigilance system to ensure sustainability.

Challenges

- Constraints - Insufficient funding, lack of staff, and inadequate infrastructure are major obstacles to creating and sustaining a haemovigilance system.

Next steps

- Capacity Building:
  - Train healthcare workers to recognize, report, and manage adverse transfusion reactions.
- Technology Integration:
  - Use IT to efficiently collect, report, and analyze data for real-time transfusion monitoring.
- Awareness campaigns:
  - Promote haemovigilance and encourage reporting of adverse events among healthcare providers and the public to ensure safe blood transfusions.

Conclusion: Establishing a haemovigilance system in an LMIC is feasible with strategic planning, sustained commitment, and international cooperation, as demonstrated by Ghana's experience. LMICs can improve patient safety and healthcare outcomes by utilizing local strengths and addressing systemic challenges through effective haemovigilance practices to ensure decision-making that is data drivenEstablishing a haemovigilance system in an LMIC is feasible with strategic planning, sustained commitment, and international cooperation, as demonstrated by Ghana's experience. LMICs can improve patient safety and healthcare outcomes by utilizing local strengths and addressing systemic challenges through effective haemovigilance practices to ensure decision-making that is data driven.

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Development of Vaccine Related Event (VRE) Response Plan: A Case Study of Ghana

Delese Darko[1], Seth Seaneke[1], Edwin Nkansah[1], George Tsey Sabblah[1], Rhoda Ewurabena Appiah[1], Adela Ashie[1], Abena Asamoa-Amoakohene[1], Jeremiah Ewudzie-Sampson[1], Kwame Amponsa-Achiano[2], Naziru Tanko Mohammed[2]

[1]Food and Drugs Authority, Accra, Ghana. [2]Expanded Programme on Immunization- Ghana Health Service, Accra, Ghana

Introduction: Although, vaccines are safe, they may cause adverse events which may not be causally related to the vaccine or vaccination process. Each country must have systems to prepare for and respond adequately to Vaccine Related Events (VREs), to provide assurance of continued vaccines safety.[1] VRE Response Plan is a tool that provides for a coordinated response to VRE. It helps with identifying respective processes, roles and responsibilities of various stakeholders in the event of a VRE. The Food and Drugs Authority (FDA) and Expanded Programme on Immunization (EPI)- Ghana Health Service (GHS) led the development of the VRE response plan.

Aim/Objective: To describe the processes involved in the development of a VRE Response Plan.

Methods: The development process involved 4 steps:

1. identification of key stakeholders who would be involved in the drafting of the VRE response plan.
2. baseline assessment of the current reporting rate of adverse events following immunization (AEFI), procedures for addressing VRE issues, and roles of stakeholders at each level.
3. drafting of the VRE response plan.
4. simulation of a VRE response plan to assess its usefulness.

Results: Key stakeholders were identified based on interest and influence in VRE response. These included FDA, EPI, health promotion department of the GHS and communication experts.

The baseline assessment involved qualitative and quantitative methods. The quantitative approach involved a desk review to obtain data on the AEFIs received from the deployment of COVID-19 vaccines six months before the commencement of the qualitative interviews, status of investigation of serious AEFIs, capacity building programs for healthcare workers involved in safety, communication or response

activities. The qualitative study was conducted at national, district and health facility levels.

Development of the VRE response plan was jointly done by the stakeholders based on findings from the baseline assessment. Periodic meetings were held to review the document. The draft plan was presented for stakeholder review and comments included in the final draft. The plan has a background and four sections on preparing for a VRE, strengthening detection of AEFI and events of special interest, planning a response to VRE and sustaining through evaluation of response to the VRE.

A simulation of a VRE event was done to assess the usefulness of the VRE response plan.

Conclusion: Every country needs a VRE Response Plan to provides for a fast and coordinated response to VRE during vaccination programmes. The effective coordinated efforts of FDA and EPI, and engagement of stakeholders resulted in the successful development of a VRE response plan that could be used and adapted to most situations in a vaccination programme. Countries must widely disseminate VRE response plans to relevant stakeholder to ensure its utilization.

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Impact of the Med Safety App on Adverse Drug Reaction Reporting by Health Workers in Uganda: A Cluster-Randomized Controlled Trial

Ronald Kiguba[1], Helen B. Ndagije[2], Norah Mwebaza[1], Ronald Ssenyonga[3], Lilian Giibwa[3], Phil Tregunno[4], Kendal Harrison[4], Munir Pirmohamed[5]

[1]Department of Pharmacology and Therapeutics, College of Health Sciences, Makerere University, Kampala, Uganda. [2]National Pharmacovigilance Centre, National Drug Authority, Kampala, Uganda. [3]Department of Epidemiology and Biostatistics, College of Health Sciences, Makerere University, Kampala, Uganda. [4]Medicines and Healthcare products Regulatory Agency, London, United Kingdom. [5]MRC Centre for Drug Safety Science and Wolfson Centre for Personalised Medicine, Institute of Systems, Molecular and Integrative Biology (ISMIB), University of Liverpool, Liverpool, United Kingdom

Introduction: Digital innovations for pharmacovigilance should leverage the increased access to smartphones in regions with the lowest rates of suspected adverse drug reaction (ADR)-reporting worldwide, particularly in low- and middle-income countries (LMIC).[1] Med Safety is a smartphone application adapted from the prototype mobile application designed by the European Innovative Medicines Initiative.[2] Med Safety has been rolled out in several LMIC, however, its utility for ADR-reporting in these settings remains to be established.[1, 3, 4]

Aim/Objective: To determine the effectiveness of Med Safety for increasing the rate of ADR-reporting by health workers in Uganda.

Methods: This pragmatic cluster-randomized controlled trial evaluated Med Safety at sites offering combination antiretroviral therapy (cART). In all, 382 sites were randomly assigned to the intervention (Med Safety) and comparison arms. Each site, a cluster, consisted of health workers and individuals receiving dolutegravir-based cART. In the intervention arm, health workers were trained to use mobile-, paper- and web-based reporting, whilst those in the comparison arm received training in paper- and web-based reporting only. The primary outcome was the rate of ADR-reporting to Uganda's National Pharmacovigilance Centre as the number of ADR-reports filed by health workers per 100,000 person-months of individuals receiving dolutegravir-based cART, per study arm. Unadjusted and regression-adjusted ADR-reporting rates were computed. The outcome was analysed with mixed effects negative binomial regression to account for clustering, the large number of sites that did not report, and, the skewed distribution for sites that reported. This trial is registered with the Pan African Clinical Trials Registry, number PACTR202009822379650.

Results: From August 2020 to October 2022, we enrolled 367 (96%) of 382 randomized sites, with 2464 health workers, into two arms: 184 sites in the intervention (n = 1253), and 183 sites in the comparison arm (n = 1211). About half the sites (56%, 205/367) did not file any ADR-report. For sites that reported, the median ADR-reporting rate was 12 reports per 100,000 person-months of follow-up (13.5 in Med Safety; 10.6 in comparison). The regression-estimated baseline ADR-reporting rate for all sites was 3.8 reports per 100,000 person-months (6.6 in Med Safety; 1.0 in comparison). The ADR-reporting rate for *all ADR reports* was 73% higher in the Med Safety arm versus comparison arm (incidence rate ratio, IRR of 1.73; 95% confidence interval, CI = 1.26, 2.37: p-value = 0.001); and 92% higher for *dolutegravir-related ADR reports* (IRR of 1.92; 95% CI = 1.42, 2.60: $p<0.001$). The intervention effect persisted for 24 months.

Conclusion: Med Safety showed significant and durable improvement in the rate of ADR-reporting. Med Safety should be scaled up to promote digital pharmacovigilance in LMIC.

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Safety and Risk-Management in Clinical Trials with Tissue Regenerative Products

Nolan Joyce[1,2], Connor Roddy[1,2], Marina Malikova[1,2]

[1]Boston University, Boston, USA. [2]Boston Medical Center, Boston, USA

Introduction: Chronic wounds (e.g. diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs)) have increased interest for research due to the high financial burden on healthcare systems. [1, 2] It is necessary to maintain balance between efficient study conduct and patient safety. It was hypothesized that in clinical trials at a tertiary care safety net hospital patients' burden is high and adverse events are common in diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs)

populations. Social determinants of health play a role in medication adherence in clinical trials and chronic disease management that may increase risk if not managed correctly. [3, 4]

Aim/Objective: We aimed to assess safety profile of patients enrolled in tissue-regenerative clinical trials; examine underlying causes in order to develop risk and safety mitigation strategies for wound care clinical trials with tissue-regenerative products.

Methods: Data obtained from 258 subjects were analyzed retrospectively. Correlations between social determinants of health (SDH) (i.e. race, gender, socioeconomic status, distance traveled, etc.) and adverse events (i.e. rate of adverse events, type of adverse event, relatedness, expectedness, severity, etc.) were assessed by using Wilcoxon Scores and Kruskalis-Wallis tests.

Results: Overall, the DFU group was noted to have higher prevalence of serious adverse events (SAEs) (22.8% of enrolled subjects) and adverse events (AEs) (78.3% of enrolled subjects) as compared to VLU group with 12.4% of SAE and 71.0% AEs observed in the study population. Kruskalis-Wallis test demonstrated statistically significant correlation between polypharmacy (5+ drugs) and higher number of adverse events ($p = 0.0016$). Additionally, a Spearman correlation test showed that a higher number of co-morbidities was associated with a higher number of adverse events ($p = 0.0007$). These findings were statistically significant. Also, a larger number of SAEs per patient were detected for DFU etiology, and these events were more severe and diverse as compared to patients with VLUs.

Conclusion: These findings in polypharmacy and co-morbidities being associated with a higher number of adverse events highlighted the importance of safety monitoring of patients with high disease burden in clinical trials. Understanding the frequency and types of adverse events can provide important insights for those conducting trials in a particular indication. Additionally, monitoring can help to address social determinants that contribute to higher numbers of adverse events, and proactively address disease burden with appropriate medical management to minimize risks in tissue regenerative clinical trials.

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Impact of Social Determinants of healTh on Safety of Patients in Device Clinical Trials Conducted at a Safety-Net Hospital

Anna Schneider[1,2], Katherine Cilley[1,2], Marina Malikova[1,2]

[1]*Boston University, Boston, USA.* [2]*Boston Medical Center, Boston, USA*

Introduction: Representation of diverse groups in device clinical trials is necessary in order to provide innovative patient-centric solutions and achieve health equity. [1] The FDA has issued guidelines that recommend to include diverse populations of patients into clinical trials with various social determinants of health (SDH) [2, 3], which encompass factors that contribute to a patient's health and trial outcomes. [4, 5] In clinical trials, adverse events (AEs) and protocol deviations (PDs) highlight areas where safety, efficacy, and quality can be improved. [6]

Aim/Objective: To evaluate how social determinants correlate with safety events in medical device clinical trials in order to identify safety signals, improve safety profile, and develop risk-based safety and quality management strategies.

Methods: Data obtained from 221 patients randomized into a device clinical trials were assessed retrospectively. The relationship between several SDH variables (i.e. race, sex, socioeconomic status, type of insurance, distance traveled, comorbidities, polypharmacy, etc.) and PDs, as well as to AEs, was examined using Spearman correlation and Kruskalis-Wallis tests.

Results: Spearman correlation test demonstrated that older age was associated with higher number of AEs ($p = 0.0129$), higher number of PDs ($p = 0.0105$), and higher dropout rates ($p = 0.0001$). The longer distance a patient had to travel to their visits was associated with the higher number of PDs ($p = 0.0212$). Out of 697 adverse events reported in these device clinical trials, 93.4% were not related to the device, and 81.6% were not related to the procedure. Furthermore, the number of comorbidities was significantly associated with the higher number of AEs ($p = 0.001$) and more deviations ($p = 0.0157$). Additionally, with more comorbidities it was more likely a patient would drop out from the study ($p = 0.001$). Higher number of concomitant medications/ polypharmacy were associated with the higher number of AEs ($p = 0.038$).

Conclusion: Older age, higher number of comorbidities, and polypharmacy were associated with increased number of AEs, PDs, and study drop out. Examining the root causes of these outcomes, as well as the patient-centric medical management, can improve data integrity and aid risk-based safety and quality management in device clinical trials.

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Factors Associated with Immune-Related Adverse Events in Immune Checkpoint Inhibitor Users

Sun-Young Jung, Dal Ri Nam, Yu-seon Jung, Jongmin Lee, Eunji Kim

Chung-Ang University, Seoul, Korea, Republic of

Introduction: Although immune checkpoint inhibitors (ICIs) have significantly contributed improved survival among patients with advanced cancer, Immune-related adverse events (irAEs) following the use of ICIs is a major safety concern.
Aim/Objective: To identify factors associated with irAEs among ICI users in a population-based cohortTo identify factors associated with irAEs among ICI users in a population-based cohort
Methods: A retrospective cohort study was conducted using the Korean National Health Insurance claims database. ICIs anti-CTLA-4 (Ipilimumab), anti-PD-1 (Nivolumab, Pembrolizumab), and anti-PD-L1 (Atezolizumab, Avelumab, Durvalumab). The incident ICI users between January 2018 and June 2022, excluding those with a history of brain, bone, or bone marrow metastases were followed up to incidence of irAE, death, or December 2022. An irAE in ICI user cohort was defined as the first claim of steroid prescription with a daily dose ≥25mg/day (prednisone equivalent dose) or PO corticosteroid (CS) of ≥30 days or IV CS of ≥3 times. Logistic regression analysis was performed to calculate odds ratio (OR) and 95% confidence interval (CI) of factors associated with irAE.
Results: The irAEs occurred in 1,680 (7.96%) out of the 21,114 ICI user cohort. Male sex(aOR 1.38 (95% CI 1.20-1.59)), older age, lung cancer (aOR 1.94 (95% CI 1.49-2.53)), history of psoriasis (aOR 1.43 (95% CI 1.08-1.89)) were associated with incidence of irAE.
Conclusion: This study identified factors associated with irAE among ICI user in Korean population. Further research considering recent advance of treatment regimens of ICIs is needed.This study identified factors associated with irAE among ICI user in Korean population. Further research considering recent advance of treatment regimens of ICIs is needed.
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Assessment of adverse Events due to BBIBP-CorV Vaccine in a Peruvian Pharmacovigilance Center

L. Yesenia Rodriguez[1], Raquel Delgado[2], Tania Solis Yucra[2], Enrique Cachay[3]

[1]Universidad Científica del Sur, Lima, Peru. [2]Seguro Social del Peru, Lima, Peru. [3]Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru

Introduction: The World Health Organization (WHO) and the 42nd Global Advisory Committee on Vaccine Safety highlighted the importance of developing systems of surveillance of the safety of the COVID-19 vaccine to identify and quantify adverse events following immunization (AEFI) and adverse events of special interest (AESI). BBIBP-CorV, an inactivated vaccine against COVID-19 developed by Sinopharm/China National Pharmaceutical Group, was first introduced in Peru. In February 2021, immunization with the BBIBP-CorV vaccine started among health personnel, and pharmacovigilance activities in the Social Security of Health of Peru (EsSalud) were implemented to understand the safety profile of BBIVP-CorV in a real-world context.
Aim/Objective: To characterize adverse events following immunization (AEFI) and to identify/quantify adverse events of special interest (AESI) possibly related to BBIVP-CorV between February 9 and August 21, 2021.
Methods: We developed a secondary analysis from the Pharmacovigilance database to calculate the AEFI reporting rate per 100,000 doses of the BBIBP-CorV vaccine. AEFI proportions by gender and age groups were compared using Fisher's exact test. In addition, a multidisciplinary team of clinicians and epidemiologists assessed the potential AESI cases following the Brighton Collaboration case definition using electronic medical records. Finally, we performed a causality assessment of serious AEFI and AESI using the software elaborated by WHO.
Results: A total of 4376 AEFI were identified from 216,736 total doses of BBIBP-CorV administered to personnel of EsSalud, corresponding to the 2019 AEFI reporting rate per 100,000 doses. Systemic symptoms were the most reported, particularly nervous system disorders. In both doses, AEFI occurred more frequently in women compared to men (2.33% vs 1.29%; p = 0.025). Regarding age, those between 40-65 years reported more N-AESI than those <40 and > 65 years (0.52% vs 0.47% vs 0.04%; p = 0.001). Over 25 AEFI (1.2%) were classified as serious adverse events (SAE). After clinical evaluation, 23 met the AESI definition. According to the causality assessment, only three cases of anaphylaxis were found to be associated with the BBIBP-CorV vaccine (A1). They were classified as severe, with a reporting rate of 1.4 cases per 100,000 doses.
Conclusion: BBIBP-CorV has an acceptable short-term safety profile and thus might help decrease the population's hesitancy and conspiracy beliefs. Our study presents a comprehensive clinical assessment of potential AESI and reports of serious adverse events. Pharmacovigilance is vital to ensuring that the safety profile of vaccines against COVID-19 is acceptable.
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Development and Implementation of a Health Transformational Leadership workshop to Health Care Professionals in México

Cinthya Galicia[1], Betty Duarte[2], Gabriela Jure[1], Miriam Salvador[1], Yibrahan Jimenez[1], Jorge Del Rivero[1], Erika Garay[1], Patricia Valverde[1]

[1]Pfizer, Mexico, Mexico. [2]Pfizer, San Jose, Costa Rica

Introduction: In health institutions, physicians or other healthcare professionals frequently occupy senior management positions; their expertise is primarily focused on technical knowledge and soft skill frequently are put aside. The transition from clinician to leader can be challenging, and without proper support, there is a risk that a great healthcare professional might not automatically make a great leader. It is important to recognize the impact that leadership can have on administration and organization, and to provide the necessary training and support to those taking on these critical roles. (1,2)
Aim/Objective: To develop a customized leadership workshop aimed at health environment according to the needs, objectives and leadership structure of Health Institutions with the objective of providing principles of transformational leadership to boost the development of sustainable interventions and intersectoral partnerships that operate across different sectors and institutional spheres of the health system. To address health challenges and create projects
for the benefit of public health and benefit of patients in México
Methods: Kick off meetings were held with the participating health care institutions in order to know the challenges they faced, once the information was collected, the material for the leadership workshop was carried out by carrying out the face -to -face workshop involving all the operational areas that participate in a way direct or indirect with the pharmacovigilance area and touching real and practical issues and its possible solution from the transformational leadership perspective.
Results: During may 2023 to december 2023 were trained Pharmacovigilance and Pharmacy services Units of 15 health care institutions around Mexican Republic (Guadalajara, Tijuana, Monterrey and Mexico City)
Conclusion: This initiative will generate the bases to recognize the importance of collaborative work under the transformational leadership scheme and will be preceding improvement projects for patients and health institutions in Mexico

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Pharmacovigilance Activities for the Early Detection of Drug-Related Problems (DRPs) on Antibiotic Therapy in Hospitalized Pediatric Patients an Integral Part of an Antimicrobial Stewardship Program (ASP)

Liliana Vargas-Neri, Dulce Daniela Blanco-Vega, Tania Salazar-Alva, Xuxek Becerril-Martinez, Daniela Vazquez-Aldana, Jocelyn Jacobo-Mendoza, Rodolfo Jimenez-Juárez, Group of Collaboration

Hospital nfantil de México Federico Gómez, Mexico City, Mexico

Introduction: Antimicrobials are the most prescribed and most misused drugs in hospitals. This is of particular concern in pediatric populations where pharmacodynamic, and pharmacokinetic changes should be especially considered as 30-40% of pediatric patients suffer at least one drug related problem (DRP). These problems can potentially lead to increased antimicrobial resistance, morbidity, prolonged hospital stays, and increased healthcare costs.
Aim/Objective: To demonstrate the detection and analysis of drug-related problems on antibiotics prescribed to hospitalized pediatric patients as part of an ASP and their impact on patient safety.
Methods: Descriptive study of the maneuver of the pharmaceutical audit/feedback interventions carried out prospectively in the period from January to December 2023, where the appropriateness of antibiotics prescribed to hospitalized patients in the Hemato-oncology service of the Federico Gómez Children's Hospital of Mexico was evaluated through the review of physical and electronic records in conjunction with the information provided by the health professionals in charge of the patients. Following the evaluation of the appropriateness of the prescription, the pertinent recommendation/feedback actions were emitted.
Results: The appropriateness of 1014 prescribed antibiotics for 395 hospitalized patients in the Hemato-oncology service of the Federico Gómez Children's Hospital in Mexico was evaluated, corresponding to 464 infectious events. A total of 224 drug-related problems were found, of which 82 were subtherapeutic doses (36.6%), 62 were antibiotic discontinuations (27.6%) due to unnecessary treatment, 43 were related to supra-therapeutic doses (19.1%), 12 involved antibiotic changes (5.3%), 8 were antibiotic discontinuations due to process errors (3.5%), 7 were due to incorrect administration frequency (3.1%), 7 were related to a new indication of antibiotic(3.1%), 2 were due to incorrect treatment duration (0.89%), and 1 was related to epidemiological notification (0.44%). Of these, 148 pharmaceutical interventions were accepted by the prescriber (66.1%), 47 were rejected (20.9%), and 29 were not carried out (12.9%).
Conclusion: Antibiotic use-related problems were found in a substantial proportion of hospitalized pediatric patients, mainly those related with dose selection and treatment duration. Considering the impact of drug-related problems on morbidity, mortality, hospital stay and economic burden, multidisciplinary efforts are critical for the implementation of pharmaceutical interventions as an essential part of an antimicrobial stewardship program. Antibiotic use-related problems were found in a substantial proportion of hospitalized pediatric patients, mainly those related with dose selection and treatment duration. Considering the impact of drug-related problems on morbidity, mortality, hospital stay and economic burden, multidisciplinary efforts are critical for the implementation of pharmaceutical interventions as an essential part of
an antimicrobial stewardship program.

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Enhanced Surveillance of Adverse Reactions to COVID-19 Vaccines in France: Feedback with Three Examples of Signals

Evelyne PIERRON, Mehdi Benkebil, Linda Moloney

ANSM, Saint Denis, France

Introduction: In France, the vaccination campaign was rolled out on December 27th, 2020, less than a year after the pandemic began. Priority was given to people at risk (age, health status or healthcare profession). The assessment of these vaccines to obtain a conditional marketing authorisation (MA) in record times through a rolling review process. Monitoring COVID-19 vaccines was a major challenge leading the French National Agency for the Safety of Medicines and Health Products (ANSM) to implement an enhanced surveillance system based on pharmacovigilance in conjunction with the French regional pharmacovigilance centers (CRPVs) and conducting pharmaco-epidemiological studies by EPI-PHARE [1].
Aim/Objective: To detect a potential pharmacovigilance signal and to provide a real time safety related to COVID-19 vaccines
Methods: The enhanced surveillance system includes a monitoring committee set up by the ANSM, which brings together experts from the ANSM and the CRPVs on a regular basis to analyse all the potential safety signals identified within the framework of the pharmacovigilance survey. The committee carries out a cross-analysis of these potential signals, in particular with data from clinical trials, scientific literature data, as well as European and global analyses. The ANSM, in collaboration with the CRPVs [2, 3], can issue measure at any time if a safety signal is identified.
Several types of safety signals have emerged during the vaccination campaign in France. In some cases, their occurrence was specific enough to prompt a direct reaction from the French health authorities; in other cases, it was the accumulation of weak signals at the European level that allowed a specific case to be confirmed. Three examples of these signals are described: Influenza-like illnesses associated with Vaxzevria, atypical thrombosis associated with Vaxzevria and and cardiac diseases (myocarditis, pericarditis) with messenger RNA vaccines (Comirnaty and Spikevax)
Results: Feedback from analyzing these 3 examples of signals (national or European) show that the objectives of setting up an enhanced surveillance system at national level, including a continuous assessment of vaccine safety combining pharmacovigilance and pharmaco-epidemiology, have been fulfilled. The transparency adopted by the ANSM as part of the enhanced surveillance system, with analysis reports made publicly available, has contributed to both a strong public awareness of pharmacovigilance and a strong involvement of healthcare professionals in reporting of adverse reactions.
Conclusion: This enhanced surveillance system has enshrined the principle of two complementary components of pharmacovigilance and pharmaco-epidemiology, collegiality through a multidisciplinary experts committee and transparency. The national surveillance constitutes a major brick for the surveillance performed at the European level.

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What Influences Major Influencers of COVID-19 Vaccination Decisions? Evidence from South Africa

Johanna C. Meyer[1,2], Kesentseng J. Mahlaba[1,2], Andrew M. Musyoki[3,2], Siphiwe W. Khumalo[1], Dineo V.R. Mmakgwale[1], Maria D. Kau[1], Nqobile T. Makhaza[1], Noel-David Nogbou[3], Varsetile V. Nkwinika[4,2], Maphoshane Nchabeleng[3,5,6], Rosemary J. Burnett[1,2]

[1]Department of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa. [2]South African Vaccination and Immunisation Centre, Sefako Makgatho Health Sciences University, Pretoria, South Africa. [3]Department of Microbiological Pathology, School of Medicine, Sefako Makgatho Health Sciences University, Pretoria, South Africa. [4]Department of Virology, School of Medicine, Sefako Makgatho Health Sciences University, Pretoria, South Africa. [5]Medunsa Clinical Research Unit (MeCRU), Sefako Makgatho Health Sciences University, Pretoria, South Africa. [6]National Health Laboratory Service, Dr George Mukhari Academic Hospital, Pretoria, South Africa

Introduction: The COVID-19 pandemic and accompanying misinformation has exacerbated vaccine hesitancy globally.[1] While healthcare workers (HCWs) and educators are role models and trusted sources of health information, they are susceptible to vaccine hesitancy.[2–4] Considering their influential role within communities, understanding the drivers and influencers of vaccination behaviour amongst these groups is necessary.
Aim/Objective: To investigate i) COVID-19 vaccination uptake; ii) influencers of vaccination behaviour; and iii) the antecedents of vaccination behaviour (i.e. confidence, complacency, constraints,

calculation, and collective responsibility) in South African HCWs and educators.

Methods: Five cross-sectional online surveys were conducted during the COVID-19 pandemic (2022-2023) among HCWs, school educators, academics, and support staff at a tertiary institution. The survey (available on the SurveyMonkey® platform or on Microsoft Forms) was completed by 2737 volunteers. Data were collected on demographics, COVID-19 vaccination status, influencers, and antecedents of vaccination behaviour. A Likert scale-based 16-item adaption of the 5C antecedents of vaccination behavior [5] was used. Survey data were downloaded to Microsoft Excel®, cleaned and merged. Fifteen 5C statements were scored from 1 = strongly disagree to 7 = strongly agree, while one 'Collective responsibility' item was reversed scored. Statistical analysis was performed with jamovi (Version 2.3.26). Mean 5C scores stratified by COVID-19 vaccination status were compared (Mann-Whitney U test). Odds ratios (ORs) with 95% confidence intervals (CIs) and chi-square p-values were calculated to identify statistically significant ($p<0.05$) influencers of vaccination behaviour. Ethical clearance was obtained, and respondents provided informed consent.

Results: Most respondents (n = 2737) were female (69.2 %), Black African (57.7%), <40 years (56.9%), HCWs (72.5%) and public sector employees (50.1%). Overall, 78.1 % received ≥1 COVID-19 vaccine dose/s. All items of the 5C 'Confidence' and 'Collective responsibility' constructs predicted being vaccinated against COVID-19. All items of the 'Complacency', 'Calculation' and 'Constraints' constructs predicted being unvaccinated against COVID-19. Being influenced by social media (OR: 0.41; 95% CI: 0.32- 0.52; $p<0.001$) and the internet (OR: 0.35; 95% CI: 0.28-0.44; $p<0.001$) were barriers to COVID-19 vaccine uptake, while being influenced by colleagues (OR: 1.63; 95% CI: 1.3-2.04; $p<0.001$), healthcare professionals (OR: 1.53; 95% CI: 1.23-1.9; $p<0.001$) and the government (OR: 2.45; 95% CI: 1.91-3.15; $p<0.001$) were predictors of COVID-19 vaccine uptake.

Conclusion: One in five respondents were not vaccinated against COVID-19, with social media and the internet being the main influencers of this negative vaccination behaviour. The adapted 5C scale was useful for predicting COVID-19 vaccination behaviour and can be further adapted and validated for South Africa. One in five respondents were not vaccinated against COVID-19, with social media and the internet being the main influencers of this negative vaccination behaviour. The adapted 5C scale was useful for predicting COVID-19 vaccination behaviour and can be further adapted and validated for South Africa.

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Signal Detection and Management for Vaccines

Preeti Kharb[1], Deepak Polpakara[1], Pawan Kumar[2], Satinder Aneja[3], Rakesh Aggarwal[4]

[1]AEFI Secretariat, Immunization Technical Support Unit, New Delhi, India. [2]Ministry of Health and Family Welfare, New Delhi, India. [3]Lady Hardings Medical College, New Delhi, India. [4]JIPMER, Puducherry, India

Introduction: The evaluation of safety signals is part of vaccine vigilance and is essential to ensure that regulatory authorities and immunization programmes have the most up-to-date information on benefits and risks. The dynamic balance may change over time and may impact pharmacovigilance activities.

Aim/Objective: In public health programmes, the system-setting process is an evolving mechanism per the needs of public health programmes. The objective of the signal management system is to continuously conduct risk-benefit assessments of vaccines and provide recommendations to vaccine vigilance stakeholders.

Methods: The rapid detection of vaccine safety signals of global importance is complemented by a scientifically sound assessment of the signals through the signal management process performed to determine whether there are new risks associated with a vaccine or whether known risks have changed and includes any related recommendations, decisions, communications and tracking. Specifically, in resource-limited settings, 'Signal Detection' is usually done using the traditional approach. Using the traditional and disproportionality analysis along with MedDRA tools for establishing a Signal Management System. A Signal Management Framework for Adverse Event Following Immunization (AEFI) as part of the overall vaccine safety surveillance system for India has been established to strengthen vaccine safety surveillance.

Results: Minor, serious and severe AEFIs are reported, investigated and causality assessment is conducted as part of AEFI surveillance system. Dedicated processes and structures for conducting safety signal management for vaccines were set up. The evidence generated by the system equips the decision-makers to take important decisions to ensure vaccines administered under the programme are safe. Signal management and safety monitoring is also part of 'National AEFI Surveillance and Response guidelines 2024' & 'COVID-19 Vaccines Operational Guidelines' published by Ministry of Health and Family Welfare (MOHFW). A signal review panel (SRP) constituted at the national level reports its findings and recommendations to the National AEFI Committee and MOHFW. The AEFI Secretariat analyses the data and presents it to the SRP and follows up on the recommendations of the SRP. The regulatory recommendations from the signal review panel are shared with CDSCO to be shared with Marketing Authorization Holders (MAHs) for further action such as inclusion of recommended adverse events in the Summary of Product Characteristics for the said vaccine.

Conclusion: Signal management is an important aspect of a mature pharmacovigilance system at national-level since the considerations

of risk-benefit impact on public health are kept in mind throughout the decision-making process.

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Assessment of Severe Adverse Effects of a Dietary Supplement Containing Resveratrol and Quercetin Dihydrate

Nouzha Lazli, Rima Sehab, Aziza Saci

National center of pharmacovigilance and materiovigilance, Algiers, Algeria

Introduction: Two reports of severe adverse effects, including one fatality, were received by the National Center of Pharmacovigilance and Materiovigilance of Algeria (CNPM), prompting scientific scrutiny to assess their association with the use of containing Resveratrol and Quercetin dihydrate, as adjunctive therapy for respiratory conditions

Aim/Objective: To assess the causality link between the dietary supplement and severe adverse effects.

Methods: Due to the lack of essential data to evaluate the causality link and severity of reported effects (one death and one case involving or prolonging hospitalization), an investigation was initiated by the CNPM. This involved sending the CNPM's "patient dossier" form to the investigating physician to complete missing information for both cases.

For both dietary supplements , the Nutrivigilance method of ANSES was used due to notable differences between dietary supplements and drugs (lack of demonstrated benefit and safety studies).

This Nutrivigilance method allows for determining intrinsic and extrinsic imputability scores. The patients were on other medications, and another herbal dietary supplement was also administered. Only the results related to Resveratrol and Quercetin dihydrate are presented here."

Results: The chronological scores are C2 for both cases, indicating a compatible timing with the onset of adverse effects. The etiological score is E0 as another cause, a flu-like syndrome in a diabetic patient with post-COVID-19 lung lesions, was identified. The intrinsic imputability score is I1, with outpatient follow-up and death reported to the treating physician without a differential diagnosis. The extrinsic imputability score is B0, with no reported toxicity in clinical, animal, or case studies for the active ingredients in both dietary supplements.

Conclusion: The evaluation of severe adverse effects of (Resvératrol/Quercétine dihydrate) needs further investigation into its safety profile. The Nutrivigilance method used provides insights into the potential causality link, emphasizing the importance of continuous monitoring of dietary supplements' safety. Future studies should focus on elucidating the mechanism of adverse effects and optimizing risk management strategies.The evaluation of severe adverse effects of (Resvératrol/Quercétine dihydrate) needs further investigation into its safety profile. The Nutrivigilance method used provides insights into the potential causality link, emphasizing the importance of continuous monitoring of dietary supplements' safety. Future studies should focus on elucidating the mechanism of adverse effects and optimizing risk management strategies.

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Standardizing QPPV Training in Africa: Development and Implementation of a Comprehensive Curriculum and Objective Assessments for Enhanced Pharmacovigilance Competency

Sharon Laryea[1], Delese Darko[2], Adela Ashie[2], Abena Amoakohene[2], Bernice Owusu-Boakye[1], Alexander Dodoo[1]

[1]African Collaborating Centre for Pharmacovigilance and Surveillance, Accra, Ghana. [2]Food and Drugs Authority, Accra, Ghana

Introduction: The Qualified Person for Pharmacovigilance (QPPV) is a pivotal role mandated by regulatory authorities for personnel who assure the safety and efficacy of medicinal products for marketing authorization holders (MAHs). Despite the critical importance of QPPVs, there is no formalized curriculum for their training in most countries. This gap in formal training leads to inconsistencies in competency of QPPVs. In Africa, the need for robust pharmacovigilance (PV) systems is acute due to high disease burden and influx of pharmaceutical products necessitating rigorous safety monitoring to protect public health. There is therefore the need for a standardized QPPV curriculum in Africa.

Aim/Objective: The objective of this study is to develop and deploy a formal training programme for QPPVs in Ghana as a prerequisite for designation as QPPVs and to examine uptake of the programme.

Methods: The African Collaborating Centre for Pharmacovigilance and Surveillance (ACC), Ghana and the Ghana Food and Drugs Authority (FDA), developed a formal QPPV curriculum for training and assessment of prospective QPPVs.

The comprehensive standardized curriculum was based on the European Medicines Agency Guidelines on good pharmacovigilance practices (GVP), the enabling Act of the Food and Drugs Authority, i.e., the Public Health Act, 2012 (Act 851) and the FDA's published guidelines on PV. The curriculum covered 9 modules including: Introduction to PV; Qualified Person for Pharmacovigilance; Pharmacovigilance Quality Systems; Individual Case Safety Reports, data management, coding and case causality assessment; Pharmacovigilance methods; Signals and Signal Management; Communication and Crisis Management in Pharmacovigilance; Periodic Safety Update Reports and Risk Management Plans; and Pharmacovigilance Audits and Inspections. It is deployed over a 2-week in-person theoretical and hands-on training session with pre- and post- assessment of participants. Continuous formal objective assessments were also incorporated using validated evaluation tools and methodologies to measure trainees' knowledge and skills.

Results: The ACC (currently, the only approved training institution for QPPVs in Ghana) has organized 13 QPPV training courses from 2015 to 2023. Two hundred and fifteen would-be QPPVs have been trained including 66 females (30%). Participants included pharmacists, physicians and regulatory affairs practitioners. Participants came Ghana (over 90%), Kenya, Liberia, Nigeria, Uganda, the UK and Zambia. One hundred and thirteen (53%) of all trainees were designated as QPPVs by the FDA.
Conclusion: The ACC and the FDA in Ghana have developed and deployed a formal QPPV training programme for training and competence assessment of personnel prior to designation as QPPVs in Ghana. This model supports the development of highly skilled pharmacovigilance professionals who are assessed based on objective, standardized criteria. The approach offers a replicable approach for regions seeking to enhance pharmacovigilance training and practices.
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Evaluating The Risk of Cardiac Arrhythmia in Patients Taking Sodium Channel Blockers Using Real World Data in Korea

Nayeong Son, Jieun Lee, Myungsik Yoo, Bonggi Kim

Korea Institute of Drug Safety and Risk Management, Anyang, Korea, Republic of

Introduction: In March 2021, the FDA issued a safety communication highlighting an increased risk of cardiac rhythm problems in patients taking lamotrigine, a widely used sodium channel blocker (SCB) [1]. While some studies have evaluated the association between SCBs and cardiac arrhythmia, real world evidence (RWE) in Korean population remains insufficient.
Aim/Objective: To compare the risk of cardiac arrhythmia among specific SCB users to that of carbamazepine usersTo compare the risk of cardiac arrhythmia among specific SCB users to that of carbamazepine users.
Methods: We conducted a retrospective new-user cohort study of single SCB users from 2016 to 2020, using two data sources: the electronic health record-based common data model (CDM) [2] from 13 data partners and nationwide claims data from the National Health Insurance Service (NHIS-DB) [3]. The study population was followed from the day after the first SCB prescription for up to two years. Follow-up ended upon the occurrence of cardiac arrhythmia, death or a switch in SCB medication. We calculated the incidence rate and hazard ratio (HR) using a Cox proportional hazards model with 1:1 propensity score matching to compare the risk of cardiac arrhythmia among specific SCB users against carbamazepine users. Meta-analyses were performed to combine site-specific estimates from CDM data partners.
Results: In the CDM data, 665 out of 26,327 SCB users experienced cardiac arrhythmia (15.6 per 1,000 person-years). In the NHIS-DB, 4,806 out of 348,889 SCB users experienced cardiac arrhythmia (7.8 per 1,000 person-years). There was no significant difference in the risk of cardiac arrhythmia between lamotrigine and carbamazepine users (Table 1). Subgroup analysis of patients without epilepsy and without anti-arrhythmic drug use showed a significantly higher risk of cardiac arrhythmia in fosphenytoin and phenytoin users (Table 1).
Conclusion: This study identified the comparative risk of cardiac arrhythmia among specific SCBs compared to carbamazepine. The higher risk observed in fosphenytoin and phenytoin users could be due to these drugs being administered intravenously in high doses during status epilepticus to patients with a high underlying risk of cardiac arrhythmia. Despite conflicting findings in recent studies regarding the cardiac risk of lamotrigine,[4–6] which often compare past users with current users or users with non-users, this study identifies the risk by comparing specific SCB users to carbamazepine users. Given that the labels of other SCBs, except lamotrigine, include warnings about cardiac risk in Korea, our findings emphasize the importance of RWE on the cardiac risk associated with lamotrigine use.

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Table I. HR and 95% confidence interval for the risk of cardiac arrhythmia among specific SCBs users against carbamazepine users

Ingredient	Total study population	Subgroup analysis	
		without epilepsy	without anti-arrhythmic drug use
CDM			
Lamotrigine	0.90 (0.71-1.15)	0.77 (0.57-1.05)	0.84 (0.65-1.08)
Fosphenytoin	5.78 (2.38-14.08)**	5.73 (2.36-13.96) **	5.78 (2.38-14.08) **
Phenytoin	1.92 (1.27-2.90) **	2.86 (1.92-4.25) **	2.06 (1.28-3.31) **
NHIS-DB			
Lamotrigine	1.09 (0.78-1.51)	0.97 (0.75-1.26)	0.99 (0.78-1.25)
Fosphenytoin	1.21 (0.95-1.55)	3.16 (1.82-5.47) **	2.94 (1.71-5.04) **
Phenytoin	0.74 (0.71-0.77) **	1.62 (1.39-1.88) **	1.65 (1.42-1.91) **

** p-value < 0.05

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