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The Harms of Antipsychotic Drugs: Evidence from Key Studies

Thomas J. Moore, Curt D. Furberg

ABSTRACT

This safety assessment provides a detailed analysis of key studies and focuses on the six most widely used antipsychotic drugs. Lines of evidence include mechanisms of action, short-term treatment of psychosis, relapse prevention, early intervention in schizophrenia, long-term comparisons between first- and second-generation agents, and flexible treatment algorithms. Despite the diversity of study settings, several common features were seen. All the agents obstruct normal signaling through widely dispersed dopamine D2 receptors. Treatment failure or psychosis relapse was the most frequent outcome in most key studies, ranging from 38 to 93%. High discontinuation rates caused most trials to fail to demonstrate a substantial treatment benefit, or difference from an active comparator. Assessment of harm to the extrapyramidal motor system was confounded because of extensive neurological impairment from previous antipsychotic drug treatment measured at baseline, abrupt discontinuation effects, and high rates of concomitant medications to manage drug adverse effects. Claims that second-generation antipsychotic drugs have safety advantages over classical neuroleptic drugs and prevent relapse were not supported in these key studies. The extent of injury to and impairment of multiple body systems caused by antipsychotic drugs shows the need for a scientific, clinical, and regulatory reappraisal of the appropriate use of these agents.

Disclaimer: The prescription information in Table 1 was obtained under license from the IMS Health Incorporated National Prescription Audit (2015). The statements, findings, conclusions, views, and opinions expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

Pharmaceutical Benefit–Risk Communication Tools: A Review of the Literature

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ABSTRACT

This paper reviews the main tools for communicating benefit–risk medicines information to patients that are used, or could be used, by pharmaceutical regulators. One highly successful tool from the food safety sector (front-of-package traffic-light labelling) and the mental models approach (which provides a framework for developing new tools) are also reviewed as they show great promise for being usefully adapted to the pharmaceutical context. The evolution of benefit–risk medicines communication is first contextualised within the broader risk communication literature. Three distinct goals are then made explicit before critically examining the evidence for and against tools developed in the US (e.g. at the Food and Drug Administration [FDA]) and Europe (e.g. at the European Medicines Agency [EMA]). These goals are (i) sharing information (e.g. publishing clinical trial and adverse event data online); (ii) changing patients' beliefs by conveying factual knowledge (e.g. patient information leaflets and the drugs facts box); and (iii) changing behaviour (e.g. patient alert cards and warning labels). The mental models approach and traffic-light labelling, developed outside the pharmaceutical context, are then examined. Ultimately, the paper provides a helicopter view of the variety of benefit–risk communication tools that are used, or could be used, by pharmaceutical regulators in the US and Europe.

Evaluating the Safety Profile of Non-Active Implantable Medical Devices Compared with Medicines

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ABSTRACT

Recent safety issues involving non-active implantable medical devices (NAIMDs) have highlighted the need for better pre-market and post-market evaluation. Some stakeholders have argued that certain features of medicine safety evaluation should also be applied to medical devices. Our objectives were to compare the current processes and methodologies for the assessment of NAIMD safety profiles with those for medicines, identify potential gaps, and make recommendations for the adoption of new methodologies for the ongoing benefit–risk monitoring of these devices throughout their entire life cycle. A literature review served to examine the current tools for the safety evaluation of NAIMDs and those for medicines. We searched MEDLINE using these two categories. We supplemented this search with Google searches using the same key terms used in the MEDLINE search. Using a comparative approach, we summarized the new product design, development cycle (preclinical and clinical phases), and post-market phases for NAIMDs and drugs. We also evaluated and compared the respective processes to integrate and assess safety data during the life cycle of the products, including signal detection, signal management, and subsequent potential regulatory actions. The search identified a gap in NAIMD safety signal generation: no global program exists that collects and analyzes adverse events and product quality issues. Data sources in real-world settings, such as electronic health records, need to be effectively identified and explored as additional sources of safety information, particularly in some areas such as the EU and USA where there are plans to implement the unique device identifier (UDI). The UDI and other initiatives will enable more robust follow-up and assessment of long-term patient outcomes. The safety evaluation system for NAIMDs differs in many ways from those for drugs, but both systems face analogous challenges with respect to monitoring real-world usage. Certain features of the drug safety evaluation process could, if adopted and adapted for NAIMDs, lead to better and more systematic evaluations of the latter.

Vancomycin-Induced Thrombocytopenia: A Narrative Review

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ABSTRACT

Thrombocytopenia has been reported as an adverse reaction of numerous drugs. Vancomycin is often overlooked as a culprit but has been associated with several cases of thrombocytopenia that were not well described in the literature. A literature search was conducted to find reports of thrombocytopenia induced by vancomycin. Biomedical databases including 'PubMed', 'Scopus', and 'Web of Science' were searched using terms 'vancomycin', 'platelet', 'pancytopenia', 'thrombocytopenia', and 'bleeding'. English language articles published before July 2015 were included. Thirty-nine papers including 29 case reports (30 cases), five observational studies, two clinical trials, two letters, and one case series remained for final analysis. The main route of administration was intravenous infusion. This adverse reaction seems to be duration dependent with the mean time to platelet nadir count of 8 days in reported cases. The interval may be significantly shorter in re-exposure to the drug. Platelet nadir counts ranged from 2000 to 100,000/mL in patients who experienced bleeding. Vancomycin-specific antibodies were detected in 13 of 17 patients who were tested in the case reports. Based on the Naranjo Adverse Drug Reaction Probability Scale, reaction was 'definite', 'probable', and 'possible' in 1, 15, and 14 patients, respectively. Among 30 cases, vancomycin was discontinued in 29 patients and platelets returned to normal counts within 5–6 days in 17 of them; in one patient, vancomycin was not discontinued, but platelet count recovered 11 days after the nadir time. Transfusion might be recommended if severe thrombocytopenia and bleeding occurs. Intravenous immunoglobulins, corticosteroids, rituximab, and plasma exchange should be reserved for patients with resistant thrombocytopenia and severe bleeding as mentioned in a number of reports.

Proton Pump Inhibitors and Risk of Rhabdomyolysis

Scott J. Duncan, Colin W. Howden

ABSTRACT

Proton pump inhibitors (PPIs) have been associated with a variety of adverse events, although the level of evidence for many of these is weak at best. Recently, one national regulatory authority has mandated a change to the labeling of one PPI based on reports of possible associated rhabdomyolysis. Thus, in this review we summarize the available evidence linking PPI use with rhabdomyolysis. The level of evidence is insufficient to establish a causal relationship and is largely based on sporadic case reports. In general, patients with suspected PPI-associated rhabdomyolysis have not been re-challenged with a PPI after recovery. The mechanism whereby PPIs might have been associated with rhabdomyolysis is unclear but possibly related to interaction with concomitantly administered drugs such as HMG-CoA reductase inhibitors (statins). For patients with rhabdomyolysis, a careful search must be made for possible etiological factors. In patients who recover from an episode of possible PPI-related rhabdomyolysis but do not have a genuine requirement for PPI treatment, the PPI should not be re-introduced. For those with a definite indication for ongoing PPI treatment, the PPI can be re-introduced but should preferably not be administered with a statin.

Role of Preemptive Genotyping in Preventing Serious Adverse Drug Events in South Korean Patients

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ABSTRACT

Introduction: Preemptive and multi-variant genotyping is suggested to improve the safety of patient drug therapy. The number of South Koreans who would benefit from this approach is unknown.

Objective: We aimed to quantify the number of patients who may experience serious adverse drug events (ADEs) due to high-risk pharmacogenetic variants and who may benefit from preemptive genotyping.

Methods: The health claims dataset of the Korean Health Insurance Review and Assessment service for 3 % of the South Korean population for year 2011 was used to calculate the number of patients exposed to 84 drugs covered by National Health Insurance with pharmacogenomic biomarkers. The product of ADE risk-conferring genotype prevalence, ADE prevalence rates, and genotype effect sizes in South Koreans or East Asians derived from published literature and the 1000 Genomes Project, and the drug exposure data were solved to estimate the number of South Koreans in whom preemptive genotyping may prevent serious ADEs.

Results: Among 1,341,077 patients in the dataset with prescriptions, 47.4 % were prescribed a drug whose response was affected by genetic variants and 31.9 % were prescribed at least one drug with serious ADEs modulated by these variants. Without genetic testing, the number of South Korean patients predicted to experience serious ADEs due to their higher ADE risk genotypes was estimated at 729. Extrapolating this to the total South Korean population indicated that approximately 24,300 patients in 2011 might have benefitted from preemptive genotyping.

Conclusions: This study quantified the number of South Korean patients predicted to have serious ADEs and demonstrated the need for preemptive genotyping to assist safer drug therapy in South Korea.

Current Safety Concerns with Human Papillomavirus Vaccine: A Cluster Analysis of Reports in VigiBase

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ABSTRACT

Introduction: A number of safety signals—complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and chronic fatigue syndrome (CFS)—have emerged with human papillomavirus (HPV) vaccines, which share a similar pattern of symptomatology. Previous signal evaluations and epidemiological studies have largely relied on traditional methodologies and signals have been considered individually.

Objective: The aim of this study was to explore global reporting patterns for HPV vaccine for subgroups of reports with similar adverse event (AE) profiles.

Methods: All individual case safety reports (reports) for HPV vaccines in VigiBase® until 1 January 2015 were identified. A statistical cluster analysis algorithm was used to identify natural groupings based on AE profiles in a data-driven exploratory analysis. Clinical assessment of the clusters was performed to identify clusters relevant to current safety concerns.

Results: Overall, 54 clusters containing at least five reports were identified. The four largest clusters included 71 % of the analysed HPV reports and described AEs included in the product label. Four smaller clusters were identified to include case reports relevant to ongoing safety concerns (total of 694 cases). In all four of these clusters, the most commonly reported AE terms were headache and dizziness and fatigue or syncope; three of these four AE terms were reported in >50 % of the reports included in the clusters. These clusters had a higher proportion of serious cases compared with HPV reports overall (44–89 % in the clusters compared with 24 %). Furthermore, only a minority of reports included in these clusters included AE terms of diagnoses to explain these symptoms. Using proportional reporting ratios, the combination of headache and dizziness with either fatigue or syncope was found to be more commonly reported in HPV vaccine reports compared with non-HPV vaccine reports for females aged 9–25 years. This disproportionality remained when results were stratified by age and when those countries reporting the signals of CRPS (Japan) and POTS (Denmark) were excluded.

Conclusions: Cluster analysis reveals additional reports of AEs following HPV vaccination that are serious in nature and describe symptoms that overlap those reported in cases from the recent safety signals (POTS, CRPS, and CFS), but which do not report explicit diagnoses. While the causal association between HPV vaccination and these AEs remains uncertain, more extensive analyses of spontaneous reports can better identify the relevant case series for thorough signal evaluation.

The Role of Hemoglobin Laboratory Test Results for the Detection of Upper Gastrointestinal Bleeding Outcomes Resulting from the Use of Medications in Observational Studies

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ABSTRACT

Introduction: The identification of upper gastrointestinal (UGI) bleeding and perforated ulcers in claims data typically relies on inpatient diagnoses. The use of hemoglobin laboratory results might increase the detection of UGI events that do not lead to hospitalization.

Objectives: Our objective was to evaluate whether hemoglobin results increase UGI outcome identification in electronic databases, using non-steroidal anti-inflammatory drugs (NSAIDs) as a test case.

Methods: From three data partner sites within the Mini-Sentinel Distributed Database, we identified NSAID initiators aged ≥18 years between 2008 and 2013. Numbers of events and risks within 30 days after NSAID initiation were calculated for four mutually exclusive outcomes: (1) inpatient UGI diagnosis of bleeding or gastric ulcer (standard claims-based definition without laboratory results); (2) non-inpatient UGI diagnosis AND ≥3 g/dl hemoglobin decrease; (3) ≥3 g/dl hemoglobin decrease without UGI diagnosis in any clinical setting; (4) non-inpatient UGI diagnosis, without ≥3 g/dl hemoglobin decrease.

Results: We identified 2,289,772 NSAID initiators across three sites. Overall, 45.3% had one or more hemoglobin result available within 365 days before or 30 days after NSAID initiation; only 6.8% had results before and after. Of 7637 potential outcomes identified, outcome 1 accounted for 21.7%, outcome 2 for 0.8%, outcome 3 for 34.3%, and outcome 4 for 43.3%. Potential cases identified by outcome 3 were largely not suggestive of UGI events. Outcomes 1, 2, and 4 had similar distributions of specific UGI diagnoses.

Conclusions: Using available hemoglobin result values combined with non-inpatient UGI diagnoses identified few additional UGI cases. Non-inpatient UGI diagnostic codes may increase outcome detection but would require validation.

Active Surveillance of Follow-on Biologics: A Prescription for Uptake

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ABSTRACT

As lower-cost versions of original biologic drugs made by different manufacturers, follow-on biologics offer the promise of meaningful savings for the US health care system and improved patient health outcomes through greater medication adherence. Fulfillment of this promise, however, is predicated on the prescribing of such products. Under state drug product selection laws, pharmacists may substitute prescriptions for brand name, small-molecule drugs with their generic equivalents, but will be indefinitely prohibited from substituting prescriptions for original biologics with their follow-on biologic counterparts given a lack of product-specific guidance on demonstrating interchangeability. Even when interchangeable follow-on biologics become available, they will face heightened barriers to substitution following the enactment of so-called carve-outs in several states. Data collected to date suggest that a substantial proportion of US physicians remain skeptical of follow-on biologics despite their long record of safe and effective use in Europe. Active surveillance of follow-on biologics within the US market using insurance claims databases can help address this skepticism and help answer key questions concerning the safety of switching between original and follow-on products or between different follow-on products, and of extrapolating to broader indications. Funding is needed to support such surveillance activities and to disseminate the findings to key stakeholders.

Should Domperidone be used as a Galactagogue? Possible Safety Implications for Mother and Child

Luc M. Hondeghem, Noël H. Logghe

ABSTRACT

Domperidone has been used as a galactagogue; however, solid evidence from an adequate sized randomized clinical trial is missing. Optimal dosage, start of treatment, length of treatment and scope of patients who can benefit also remain unknown. Although milk obtained after domperidone administration has not been shown to have untoward effects on newborns, no sufficiently large randomized clinical trial has been done to establish safety. Domperidone has repeatedly been shown to produce sudden cardiac death, starting at 30 mg/day. Because of this known cardiac effect, the use of domperidone to increase breast milk production may not be justified.

Bone Fractures with Sodium-Glucose Co-transporter-2 Inhibitors: How real is the Risk

Edoardo Mannucci, Matteo Monami

ABSTRACT

This article succinctly summarizes the available evidence on the risk of bone fractures with sodium-glucose co-transporter-2 inhibitors. The US Food and Drug Administration has strengthened the warning for canagliflozin related to the increased risk of bone fractures, and added new information about decreased bone mineral density. The agency has also said that it will evaluate the risk of bone fractures with other drugs in the sodium-glucose co-transporter-2 inhibitor class. Increases in parathyroid hormone levels and decreases in 1,25-dihydroxyvitamin D levels have been postulated as possible mechanisms. In contrast, some studies with dapagliflozin have shown no effects on bone health. Because a consensus has not been reached, we believe that an expert opinion on how to interpret the available evidence would be of great benefit for clinicians.

The Risk of Adverse Pregnancy Outcome after First Trimester Exposure to H1 Antihistamines: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: H1 antihistamines are used for the treatment of nausea and vomiting during pregnancy as well as the symptomatic relief of asthma, urticaria, allergy, and the common cold. Although they are overall felt to be safe during pregnancy, recently several studies have challenged this assumption, as millions of women are exposed to them in the first trimester.

Methods: Following the guidelines of PRISMA, a systematic review was performed to retrieve all published articles involving H1-antihistamine exposure during pregnancy. Electronic databases including PubMed and EMBASE were searched for possibly relevant articles published in any language up to December 2015.

Results: After removing duplicate publications, and excluding animal studies and studies on drug effectiveness, 342 articles were reviewed in detail and 37 studies fulfilled the inclusion criteria for the meta-analysis. In cohort studies, the risk of major malformation in the offspring of women exposed to H1 antihistamines was not higher than that of the control population (OR 1.07; 95% CI 0.98–1.16). The Q-statistic for heterogeneity of effects was not significant ($p > 0.05$, $I2 < 25\%$) and there was no evidence of publication bias. Similar results were achieved with case–control studies (OR 1.05; 95% CI 0.90–1.23). Similarly, H1 antihistamines were not associated with more spontaneous abortions (OR 1.00; 95% CI 0.83–1.20), prematurity (OR 0.96; 95% CI 0.76–1.20), stillbirth (OR 1.23; 95% CI 0.48–3.18) or low birth weight (OR 1.20; 95% CI 0.63–2.29).

Conclusions: Based on our meta-analyses, which included a large number of studies, H1 antihistamines are not associated with an increased risk of major malformation or other adverse fetal outcomes. This study provides important information to both pregnant women and their healthcare providers regarding the safety and risk of H1 antihistamine use during this sensitive time.

Investigating the Additive Interaction of QT-Prolonging Drugs in Older People Using Claims Data

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ABSTRACT

Introduction: Drugs that potentially prolong the QT interval carry the risk of life-threatening Torsades de pointes (TdP) ventricular arrhythmia.

Objective: The objective of this study was to investigate the potential additive risk for ventricular arrhythmia with concomitant prescriptions of QT-prolonging drugs.

Methods: Claims data for persons aged ≥65 years between 2010 and 2012 in Germany were analyzed and all cases hospitalized for ventricular arrhythmia were selected. In a case-crossover analysis, exposure with QT-prolonging drugs according to the Arizona Center for Education and Research on Therapeutics (AZCERT) classification of 'known,' 'conditional,' and 'possible' TdP risk was determined in respective event and control windows preceding hospitalization. Conditional logistic regression was applied to derive odds ratios (ORs).

Results: Among 6,849,622 health-insured persons, we identified 2572 patients newly hospitalized for ventricular arrhythmia. Drugs with 'known' risk were more frequently prescribed in the event window than in the control window (309 vs. 239; $P < 0.001$). The number of drugs with an attributed 'known' risk of TdP was significantly associated with hospitalization for ventricular arrhythmia (OR: 2.22; 95% confidence interval [1.51–3.25]; $P < 0.001$), while increased risk estimates were also obtained upon categorization into one and two or more drugs compared with no drugs for the combined group of drug with 'known' (1.52 [1.16–2.00]) and 'conditional' risk (2.20 [1.42–3.41]). Pairwise comparisons and trend tests based on these classification categories could not demonstrate a significantly increased risk of two or more drugs compared with one drug.

Conclusion: Beyond suitable single-drug classifications for QT-associated risk estimation, the situation when there is co-prescription of several drugs appears to be complex and may not be extrapolated to all possible multi-drug combinations.

Surveillance of Adverse Events after Seasonal Influenza Vaccination in Pregnant Women and Their Infants in the Vaccine Adverse Event Reporting System, July 2010–May 2016

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ABSTRACT

Introduction: Routine immunization of pregnant women with seasonal inactivated influenza vaccines (IIVs) is recommended in all trimesters of pregnancy. A review of the Vaccine Adverse Event Reporting System (VAERS) during 1990–2009 did not find any unexpected patterns of pregnancy complications or fetal outcomes after administration of IIV or live attenuated influenza vaccines (LAIVs). During the 2009–2010 pandemic influenza A (H1N1) vaccination campaign, a study noted that the number of VAERS reports from pregnant women who received the H1N1 2009 inactivated monovalent vaccine (n = 288) increased compared with 1990–2009 seasonal IIV pregnancy reports (n = 148).

Objectives: The objective of this study was to assess the safety of seasonal influenza vaccines in pregnant women and their infants whose reports were submitted to VAERS during 2010–2016.

Methods: We searched VAERS for US reports of adverse events (AEs) in pregnant women who received IIV or LAIV from 1 July 2010 through 6 May 2016. Clinicians reviewed reports and available medical records and assigned a primary clinical category for each report. Reports were coded as serious based on the Code of Federal Regulations.

Results: We identified 671 reports after seasonal influenza vaccines administered to pregnant women: 544 after IIV and 127 after LAIV. Serious events occurred among 61 (11.2%) reports following IIV and one (0.8%) report following LAIV. No deaths were reported. Among reports with trimester information (n = 296), IIV was administered during the first trimester in 116 (39.2%). Among IIV reports, the most frequent pregnancy-specific AE was spontaneous abortion in 62 (11.4%) reports, followed by stillbirth in ten (1.8%) and preterm delivery in six (1.1%). The most common non-pregnancy-specific AEs were injection-site reactions (55 [10.1%]). Neonatal or infant outcomes were reported in 22 (4.0%) reports, seven of which had major birth defects of different types and no neonatal deaths.

Conclusion: As in 2009–2010, no new or unexpected patterns in maternal or fetal outcomes were observed during 2010–2016.

Hepatic Cyst Infection during Use of the Somatostatin Analog Lanreotide in Autosomal Dominant Polycystic Kidney Disease: An Interim Analysis of the Randomized Open-Label Multicenter DIPAK-1 Study

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ABSTRACT

Introduction and Aims: The DIPAK-1 Study investigates the reno- and hepatoprotective efficacy of the somatostatin analog lanreotide compared with standard care in patients with later stage autosomal dominant polycystic kidney disease (ADPKD). During this trial, we witnessed several episodes of hepatic cyst infection, all during lanreotide treatment. We describe these events and provide a review of the literature.

Methods: The DIPAK-1 Study is an ongoing investigator-driven, randomized, controlled, open-label multicenter trial. Patients (ADPKD, ages 18–60 years, estimated glomerular filtration rate 30–60 mL/min/1.73 m2) were randomized 1:1 to receive lanreotide 120 mg subcutaneously every 28 days or standard care during 120 weeks. Hepatic cyst infection was diagnosed by local physicians.

Results: We included 309 ADPKD patients of which seven (median age 53 years [interquartile range: 48–55], 71% female, median estimated glomerular filtration rate 42 mL/min/1.73 m2 [interquartile range: 41–58]) developed eight episodes of hepatic cyst infection during 342 patient-years of lanreotide use (0.23 cases per 10 patient-years). These events were limited to patients receiving lanreotide ($p < 0.001$ vs. standard care). Baseline characteristics were similar between subjects who did or did not develop a hepatic cyst infection during lanreotide use, except for a history of hepatic cyst infection (29 vs. 0.7%, $p < 0.001$). Previous studies with somatostatin analogs reported cyst infections, but did not identify a causal relationship.

Conclusions: These data suggest an increased risk for hepatic cyst infection during use of somatostatin analogs, especially in ADPKD patients with a history of hepatic cyst infection. The main results are still awaited to fully appreciate the risk–benefit ratio.

Propensity Score Weighting Compared to Matching in a Study of Dabigatran and Warfarin

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ABSTRACT

Introduction: Comparing medications in observational settings requires differences in patient characteristics to be accounted for. Propensity score (PS) methods can address these differences, but PS weighting approaches may introduce bias.

Methods: Within a cohort study of anticoagulant initiators from October 2010 through to December 2012, PS values for dabigatran relative to warfarin were estimated, and study outcomes (stroke or major bleeding) among the cohort were identified. The PS was used to match initiators and results compared with those obtained using inverse probability of treatment weighting (IPTW) and standardized morbidity ratio (SMR) weighting. Hazard ratios (HRs) for study outcomes were estimated using a proportional hazards regression model.

Results: There were 23,543 dabigatran and 50,288 warfarin initiators, and matching formed 19,189 pairs (81.5% of dabigatran initiators) which resulted in a pooled stroke HR of 0.77 (95% confidence interval [CI] 0.54–1.09), and a pooled major hemorrhage HR of 0.75 (95% CI 0.65–0.87). The IPTW results for stroke (HR = 0.00; 95% CI 0.00–0.56) and major hemorrhage (HR = 0.08; 95% CI 0.08–0.10) substantially differed, while the SMR-weighted results for stroke (HR = 0.65; 95% CI 0.42–1.03) and major hemorrhage (HR = 0.73; 95% CI 0.61–0.85) differed only slightly from matching.

Conclusions: In this example, different applications of the same PS led to substantially different results, a finding that was particularly apparent with IPTW, and this was remedied by truncating extreme weights. If IPTW is used, information regarding the weights applied along with sensitivity analyses could avoid misrepresentation of study results, and would enhance their interpretation.

Developing a Crowdsourcing approach and Tool for Pharmacovigilance Education Material Delivery

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ABSTRACT

The number of pharmacovigilance professionals worldwide is increasing with a high staff turnover. There is a constant stream of new colleagues with an interest or need to learn about the discipline. Consequently, there is an increasing need for training in pharmacovigilance. An important step towards this has been made through developing and publishing the World Health Organization (WHO)-International Society of Pharmacovigilance (ISoP) Pharmacovigilance Curriculum. Using the Pharmacovigilance Curriculum effectively, it should be supplemented by providing comprehensive training material from various sources, and making the Pharmacovigilance Curriculum attractive and a high-utility product. We describe a pilot of the development and initial evaluation of a crowdsourcing tool for the provision of pharmacovigilance education material. Pharmacovigilance experts shared links to their material to sections of relevance in the hierarchy and a small group of organisations conducted an initial testing. In this pilot, we have shown the usability of such a web-based tool. The strengths of this approach include the potential for a routine 'democratic' approach to sharing educational material to a wider community and an openness for access.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of any of the organisations they are affiliated to.

Benefits and Risks of Long-Term Asthma Management in Children: Where Are We Heading

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ABSTRACT

International guidelines provide recommendations for a stepwise approach to the management of asthma in children 0–4 years old, 5–11 years old, and adolescents who are treated as adults. Therapy is aimed at two domains of control: current impairment and future risk. The long-term controller medications, inhaled corticosteroids (ICSs), ICSs in combination with long-acting β2 agonists, leukotriene receptor antagonists, and immunomodulators, exhibit different efficacies for these domains. The risk:benefit ratios of the available medications need to be carefully assessed. This review briefly presents the benefits and the potential risks of available asthma medications in children to assist the practitioner in the optimal use of asthma medications. Specifically, the systemic activity of the ICSs and how to minimize their effects on growth and adrenal activity are reviewed as well as other potential adverse effects. Dosing strategies such as intermittent therapy are also assessed.

Hyperglycaemia Induced by Novel Anticancer Agents: An Undesirable Complication or a Potential Therapeutic Opportunity

Rashmi R. Shah

ABSTRACT

Signalling pathways involving protein kinase, insulin-like growth factor 1, insulin receptors and the phosphoinositide 3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) system are critical in promoting oncogenesis. The use of anticancer agents that inhibit these pathways frequently results in hyperglycaemia, an on-target effect of these drugs. Hyperglycaemia induced by these agents denotes optimal inhibition of the desired pharmacological target. As hyperglycaemia can be treated successfully and effectively with metformin, managing this complication by reducing the dose of or discontinuing the anticancer drug may be counterproductive, especially if it is otherwise effective and clinically tolerated. The use of metformin to treat hyperglycaemia induced by anticancer drugs provides a valuable therapeutic opportunity of potentiating their clinical anticancer effects. Although evidence from randomised controlled trials is awaited, extensive preclinical evidence and clinical observational studies suggest that metformin has anticancer properties that improve overall survival in patients with diabetes and a variety of cancers. Metformin has also been reported to reverse resistance to epidermal growth factor receptor (EGFR)-inhibiting tyrosine kinase inhibitors. This review summarises briefly the role of the above signalling pathways in oncogenesis, the causal association between inhibition of these pathways and hyperglycaemia, and the effect of metformin on clinical outcomes resulting from its anticancer properties. The evidence reviewed herein, albeit almost exclusively from observational studies, provides support for a greater use of metformin not only in patients with cancer and diabetes or drug-induced hyperglycaemia but also potentially as an anticancer drug. However, prospective randomised controlled studies are needed in all these settings to better assess the effect on clinical outcomes of adding metformin to ongoing anticancer therapy.

Cancer Event Rate and Mortality with Thienopyridines: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Thienopyridines are a class of antiplatelet drugs widely used in cardiovascular disease prevention and treatment. A recent concern has come to light regarding the safety of thienopyridines because of the possible risk of malignancy. We therefore performed a systematic review and meta-analysis to evaluate the association between thienopyridine exposure and malignancy.

Methods: We searched the MEDLINE and EMBASE databases in March 2016 for studies that evaluated incident cancer and cancer mortality with and without exposure to thienopyridines. Relevant studies were identified, and data were extracted and analysed using random-effects meta-analysis.

Results: A total of nine studies (six randomised controlled trials and three cohort studies) that included 282,084 participants were included. The cancer event rate with clopidogrel and prasugrel was 3.25% and 1.58% respectively. When compared with standard aspirin or placebo, thienopyridines are not significantly associated with cancer mortality and event rate (odds ratio [OR] 1.12, 95% confidence interval [CI] 0.80–1.56, n = 3; and OR 0.92, 95% CI 0.52–1.64, n = 2, respectively. Further analyses examining clopidogrel showed no significant association with cancer event rate or malignancy-related death. When comparing prasugrel with clopidogrel, no significant association was noted for cancer event rate (OR 1.10, 95% CI 0.89–1.37, n = 2]. Subanalyses according to cancer location showed that thienopyridines are not significantly associated with malignancy mortality and/or incidence.

Conclusions: Our results suggest that there is currently insufficient evidence to suggest that thienopyridine exposure is associated with an increased risk of cancer event rate or mortality.

Effect of Medications for Gastric Acid-Related Symptoms on Total Motile Sperm Count and Concentration: A Case–Control Study in Men of Subfertile Couples from the Netherlands

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ABSTRACT

Introduction: Gastric acid-related symptoms are highly prevalent in the general population (21–40%), and more than 11% of individuals use medication for the treatment of these symptoms. The uptake of micronutrients is dependent on the gastrointestinal potential of hydrogen (pH).

Objective: We hypothesized that medication affecting gastrointestinal pH reduces the availability of B vitamins, thereby deranging one-carbon metabolism and detrimentally affecting spermatogenesis.

Methods: This explorative nested case–control study in men of subfertile couples investigated associations between medication used for gastric acid-related symptoms and semen parameters. We included 40 men using medication for gastric acid-related symptoms and 843 men not using medication. Semen analyses were performed between 70 days before and 21 days after the visit.

Results: The use of medication was associated with a twofold higher risk of a low total motile sperm count [TMSC <1 × 106, odds ratio (OR) 2.090, p = 0.049] and negatively with sperm concentration (β −0.320, p = 0.028). Red blood cell folate was positively associated with TMSC (β 0.257, p = 0.026), sperm count (β 1.679, p = 0.013) and ejaculate volume (β 0.120, p = 0.023), and total homocysteine (tHcy) was negatively associated with sperm count (β −0.077, p = 0.021).

Conclusion: Here we delineate associations between the use of medication for gastric acid-related symptoms and poor semen quality in men of subfertile couples. The use of medication for gastric acid-related symptoms is associated with a twofold higher risk of a low TMSC and a decreased sperm concentration. Although these findings warrant further research on causality, the associations between folate, tHcy and semen quality emphasize the importance of preconception counselling in male subfertility.

Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study

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ABSTRACT

Introduction: Controversy exists about an association between angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), and thiazides (TZs) and the risk of malignant melanoma (MM), and non-melanoma skin cancer—basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Objective: The aim of this study was to determine if an association exists for ACEI, ARB, or TZ exposure and skin cancers.

Methods: This was a matched cohort study using a large electronic medical records repository, the Northwestern Medicine Enterprise Data Warehouse (NMEDW). The exposed population consisted of patients with a documented order for an ACEI, ARB, or TZ with no prior history of skin cancer. The control population consisted of matched patients without documented exposure to ACEI, ARB, or TZ and no previous skin cancer. Incident MM, BCC, or SCC diagnosis by ICD-9 codes was recorded. Odds ratios (ORs) were obtained by using logistic regression analyses.

Results: Among the 27,134 patients exposed to an ACEI, 87 MM, 533 BCC, and 182 SCC were detected. Among the 13,818 patients exposed to an ARB, 96 MM, 283 BCC, and 106 SCC were detected. Among the 15,166 patients exposed to a TZ, 99 MM, 262 BCC, and 130 SCC were detected. Significant associations using ORs from logistic regression were found for MM and TZs (OR 1.82; 95% confidence interval [CI] 1.01–3.82); BCC and ARBs (OR 2.86; 95% CI 2.13–3.83), ACEIs (OR 2.23; 95% CI 1.78–2.81) and TZs (OR 2.11; 95% CI 1.60–2.79); SCC and ARBs (OR 2.22; 95% CI 1.37–3.61), ACEIs (OR 1.94; 95% CI 1.37–2.76), and TZs (OR 4.11; 95% CI 2.66–6.35).

Conclusions: A safety signal for ACEIs, ARBs, and TZs and BCC and SCC, as well as for TZs and MM, was detected. An increased awareness and education, especially for those who are at high risk for skin cancer, are warranted for patients and healthcare providers. Further exploration of such associations for these commonly used drug classes is warranted.

Proactive Regional Pharmacovigilance System versus National Spontaneous Reporting for Collecting Safety Data on Concerning Off-Label Prescribing Practices: An Example with Baclofen and Alcohol Dependence in France

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ABSTRACT

Introduction: Off-label prescribing (OLP) may raise serious safety concerns that traditional spontaneous reporting of adverse drug reactions (ADRs) may not identify in a timely manner. In France, the 'Multidisciplinary Consultation Service for Off-Label Prescribing in Addiction Medicine' (CAMTEA) is a proactive regional system established to identify ADRs associated with the OLP of baclofen for alcohol dependence.

Objective: The aim was to demonstrate, using the French pharmacovigilance database (FPVD), that CAMTEA allowed for the reporting of a substantial amount of ADRs, comparable in nature to those provided via spontaneous reporting.

Method: The 2012–2013 FPVD notifications associated with baclofen OLP were extracted. The ten most frequent types of ADRs among 'serious' and 'non-serious' reports were listed. The frequency of each type of ADR was compared between CAMTEA and spontaneous reporting, and the magnitudes of the differences were assessed using standardized differences.

Results: A total of 428 baclofen reports (1043 ADRs) were identified, among which 221 (51.64%) originated from CAMTEA. The ten most frequent ADRs in 'serious' reports were (1) confusion (17.3%), (2) seizures (11.5%), (3) drowsiness/sedation (11.5%), (4) agitation (10.9%), (5) coma (9.6%), (6) hallucinations (7.7%), (7) falls (7.1%), (8) behavioral disorders (5.8%), (9) withdrawal syndrome (5.1%), and (10) space–time disorientation (5.1%). A standardized difference of <0.2 was identified for six out of the ten most frequent 'serious' ADRs, and eight of the ten 'non-serious' ADRs.

Conclusion: A proactive regional pharmacovigilance system could collect a substantial amount of safety data on a specific OLP practice. The profile of the ADRs collected was similar to that seen in the nationwide spontaneous reporting system.

The Impact of Provider Networks on the Co-Prescriptions of Interacting Drugs: A Claims-Based Analysis

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ABSTRACT

Introduction: Multiple provider prescribing of interacting drugs is a preventable cause of morbidity and mortality, and fragmented care is a major contributing factor. We applied social network analysis to examine the impact of provider patient-sharing networks on the risk of multiple provider prescribing of interacting drugs.

Methods: We performed a retrospective analysis of commercial healthcare claims (years 2008–2011), including all non-elderly adult beneficiaries (n = 88,494) and their constellation of care providers. Patient-sharing networks were derived based on shared patients, and care constellation cohesion was quantified using care density, defined as the ratio between the total number of patients shared by provider pairs and the total number of provider pairs within the care constellation around each patient.

Results: In our study, 2% (n = 1796) of patients were co-prescribed interacting drugs by multiple providers. Multiple provider prescribing of interacting drugs was associated with care density (odds ratio per unit increase in the natural logarithm of the value for care density 0.78; 95% confidence interval 0.74–0.83; $p < 0.0001$). The effect of care density was more pronounced with increasing constellation size: when constellation size exceeded ten providers, the risk of multiple provider prescribing of interacting drugs decreased by nearly 37% with each unit increase in the natural logarithm of care density ($p < 0.0001$). Other predictors included increasing age of patients, increasing number of providers, and greater morbidity.

Conclusion: Improved care cohesion may mitigate unsafe prescribing practices, especially in larger care constellations. There is further potential to leverage network analytics to implement large-scale surveillance applications for monitoring prescribing safety.

Pre-Exposure Prophylaxis for HIV Prevention: Safety Concerns

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ABSTRACT

Available evidence supports the efficacy of pre-exposure prophylaxis (PrEP) in decreasing the incidence of human immunodeficiency virus (HIV) infection among high-risk individuals, especially when used in combination with other behavioural preventive methods. Safety concerns about PrEP present challenges in the implementation and use of PrEP. The aim of this review is to discuss safety concerns observed in completed clinical trials on the use of PrEP. We performed a literature search on PrEP in PubMed, global advocacy for HIV prevention (Aids Vaccine Advocacy Coalition) database, clinical trials registry "http://www.clinicaltrials.gov" and scholar.google, using combination search terms 'pre-exposure prophylaxis', 'safety concerns in the use of pre-exposure prophylaxis', 'truvada use as PrEP', 'guidelines for PrEP use', 'HIV pre-exposure prophylaxis' and 'tenofovir' to identify clinical trials and literature on PrEP. We present findings associated with safety issues on the use of PrEP based on a review of 11 clinical trials on PrEP with results on safety and efficacy as at April 2016. We also reviewed findings from routine real-life practice reports. The pharmacological intervention for PrEP was tenofovir disoproxil fumarate/emtricitabine in a combined form as Truvada® or tenofovir as a single entity. Both products are efficacious for PrEP and seem to have a good safety profile. Regular monitoring is recommended to prevent long-term toxic effects. The main adverse effects observed with PrEP are gastrointestinal related; basically mild to moderate nausea, vomiting and diarrhea. Other adverse drug effects worth monitoring are liver enzymes, renal function and bone mineral density. PrEP as an intervention to reduce HIV transmission appears to have a safe benefit-risk profile in clinical trials. It is recommended for widespread use but adherence monitoring and real-world safety surveillance are critical in the post-marketing phase to ensure that the benefits observed in clinical trials are maintained in real-world use.

Digitalis Use and the Risk of Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Previous epidemiological studies have indicated an increased risk of breast cancer associated with digitalis medication, though results are inconsistent. We performed this systematic review of available epidemiological studies to clarify the association between digitalis use and the risk of breast cancer.

Methods: A search of studies published through May 2016 in MEDLINE and EMBASE databases was performed, supplemented by manual searches of reference lists. The quality of the included studies was assessed, and relative risks were pooled using both random- and fixed-effect models.

Results: Three case–control studies and six cohort studies were identified. Meta-analysis generated a pooled relative risk of 1.35 (95% confidence interval 1.24–1.46) in both fixed- and random-effect models. The heterogeneity test suggested low heterogeneity across studies. The funnel plot suggested no existence of publication bias. Subgroup analysis by study design revealed an increased risk of breast cancer associated with digitalis use from cohort studies only (relative risk = 1.39, 95% confidence interval 1.27–1.52), rather than from case–control studies. Studies with adjustment for tobacco smoking or body mass index generated lower overall estimates than those not adjusted.

Conclusions: Existing epidemiological evidence regarding the association between digitalis use and the risk of breast cancer remains inconclusive and more well-designed studies are still needed.

Identification of Substandard Medicines via Disproportionality Analysis of Individual Case Safety Reports

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ABSTRACT

Introduction: The distribution and use of substandard medicines (SSMs) is a public health concern worldwide. The detection of SSMs is currently limited to expensive large-scale assay techniques such as high-performance liquid chromatography (HPLC). Since 2013, the Pharmacovigilance Department at Novartis Pharma AG has been analyzing drug-associated adverse events related to 'product quality issues' with the aim of detecting defective medicines using spontaneous reporting. The method of identifying SSMs with spontaneous reporting was pioneered by the Monitoring Medicines project in 2011.

Methods: This retrospective review was based on data from the World Health Organization (WHO) Global individual case safety report (ICSR) database VigiBase® collected from January 2001 to December 2014. We conducted three different stratification analyses using the Multi-item Gamma Poisson Shrinker (MGPS) algorithm through the Oracle Empirica data-mining software. In total, 24 preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA®) were used to identify poor-quality medicines. To identify potential SSMs for further evaluation, a cutoff of 2.0 for EB05, the lower 95% interval of the empirical Bayes geometric mean (EBGM) was applied. We carried out a literature search for advisory letters related to defective medicinal products to validate our findings. Furthermore, we aimed to assess whether we could confirm two SSMs first identified by the Uppsala Monitoring Centre (UMC) with our stratification method.

Results: The analysis of ICSRs based on the specified selection criteria and threshold yielded 2506 hits including medicinal products with an excess of reports of product quality defects relative to other medicines in the database. Further investigations and a pilot study in five authorized medicinal products (proprietary and generic) licensed by a single marketing authorization holder, containing valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine, were performed. This resulted in an output of 23 potential SSMs. The literature search identified two communications issued to health professionals concerning a substandard rivastigmine patch, which validated our initial findings. Furthermore, we identified excess reporting of product quality issues with an ethinyl estradiol/norgestrel combination and with salbutamol. These were categorized as confirmed clusters of substandard/spurious/falsely labelled/falsified/counterfeit (SSFFC) medical products by the UMC in 2014.

Conclusion: This study illustrates the value of data mining of spontaneous adverse event reports and the applicability of disproportionality analysis to identify potential SSMs.

Antibiotic-Induced Liver Injury in Paediatric Outpatients: A Case-Control Study in Primary Care Databases

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ABSTRACT

Introduction: Antibiotics are the most commonly prescribed drug class in children. Real-world data mining on the paediatric population showed potential associations between antibiotic use and acute liver injury.

Objective: We assessed risk estimates of liver injury associated with antibiotic use in children and adolescent outpatients.

Methods: A large, multi-database, population-based, case-control study was performed in people <18 years of age from two European countries (Italy and The Netherlands) during the period 2000–2008. All potential cases of liver injury were automatically extracted from three databases and then manually validated based on Council for International Organizations of Medical Sciences (CIOMS) criteria and by exclusion of all competing causes for liver injury. Up to 100 control participants were sampled for each case and were matched on index date of the event, age, sex and database. Based on prescription data, antibiotic exposure was categorized as current, recent or past use by calculating the time period between the end of prescription and the index date. Multivariate conditional logistic regression analyses were applied to calculate odds ratios (ORs) as a measure of the association (with 95% confidence interval [CI]).

Results: We identified 938 cases of liver injury and matched to 93,665 controls. Current use of overall antibiotics is associated with a threefold increased risk of liver injury compared with past use (adjusted OR [ORadj] 3.22, 95% CI 2.57–4.03). With regard to individual antibiotics, the risk is significantly increased for current use of each antibiotic ($p < 0.005$), except for azithromycin. Risk estimates vary from the lowest ORadj of 1.86 (95% CI 1.08–3.21) for amoxicillin to the highest ORadj of 24.16 (95% CI 11.78–49.54) for cotrimoxazole (i.e. sulphamethoxazole/trimethoprim) and 26.70 (95% CI 12.09–58.96) for ceftriaxone. Sensitivity analyses confirm the associations for ceftriaxone, cotrimoxazole, and clarithromycin.

Conclusion: Antibiotic-induced liver injury in children is heterogeneous across the use of individual antibiotics. When prescribing ceftriaxone, cotrimoxazole and clarithromycin in children, paediatricians should definitely be aware of their potential risk of liver injury, even if for short periods.

Evaluation of Facebook and Twitter Monitoring to Detect Safety Signals for Medical Products: An Analysis of Recent FDA Safety Alerts

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ABSTRACT

Introduction: The rapid expansion of the Internet and computing power in recent years has opened up the possibility of using social media for pharmacovigilance. While this general concept has been proposed by many, central questions remain as to whether social media can provide earlier warnings for rare and serious events than traditional signal detection from spontaneous report data.

Objective: Our objective was to examine whether specific product–adverse event pairs were reported via social media before being reported to the US FDA Adverse Event Reporting System (FAERS).

Methods: A retrospective analysis of public Facebook and Twitter data was conducted for 10 recent FDA postmarketing safety signals at the drug–event pair level with six negative controls. Social media data corresponding to two years prior to signal detection of each product–event pair were compiled. Automated classifiers were used to identify each 'post with resemblance to an adverse event' (Proto-AE), among English language posts. A custom dictionary was used to translate Internet vernacular into Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms. Drug safety physicians conducted a manual review to determine causality using World Health Organization-Uppsala Monitoring Centre (WHO-UMC) assessment criteria. Cases were also compared with those reported in FAERS.

Findings: A total of 935,246 posts were harvested from Facebook and Twitter, from March 2009 through October 2014. The automated classifier identified 98,252 Proto-AEs. Of these, 13 posts were selected for causality assessment of product–event pairs. Clinical assessment revealed that posts had sufficient information to warrant further investigation for two possible product–event associations: dronedarone–vasculitis and Banana Boat Sunscreen--skin burns. No product–event associations were found among the negative controls. In one of the positive cases, the first report occurred in social media prior to signal detection from FAERS, whereas the other case occurred first in FAERS.

Conclusions: An efficient semi-automated approach to social media monitoring may provide earlier insights into certain adverse events. More work is needed to elaborate additional uses for social media data in pharmacovigilance and to determine how they can be applied by regulatory agencies.

Effectiveness of Risk Evaluation and Mitigation Strategies (REMS) for Lenalidomide and Thalidomide: Patient Comprehension and Knowledge Retention

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ABSTRACT

Introduction: The effectiveness of patient education activities conducted within the lenalidomide and thalidomide risk evaluation and mitigation strategies (REMS) programs was evaluated by measuring understanding of serious risk and safe-use messages.

Methods: Results from mandatory knowledge, attitude, and behavior surveys and voluntary patient surveys completed between June 2012 and June 2013 were analyzed, and responses to questions relating to compliance with birth control measures and understanding of safe-use messages are presented by patient risk category.

Results: In total, 73,645 patients were enrolled into the REMS programs for lenalidomide and thalidomide and completed mandatory surveys prior to medication dispense. Of these, 2790 (3.8%) completed an additional voluntary survey. Among voluntary survey participants, for all patient pregnancy risk categories, reported compliance with birth control requirements was above 90% when starting therapy and at follow-up. At the beginning of therapy, complete compliance was 96.3%; 3 months later it was 96.4%. Patient understanding of safe-use messages was very high in all pregnancy risk groups, notably for messages repeated at each physician visit. Overall, 98.2% of patients knew that lenalidomide and thalidomide could cause birth defects, which is part of the repeated educational messaging. In contrast, 87.1% recalled that unused product should be returned to their healthcare professional, which is not included in repeated messaging.

Conclusion: The lenalidomide and thalidomide REMS programs enhance patient understanding of safe-use messages, resulting in high levels of compliance with the birth control precautions essential to prevent fetal exposure to these known and potential human teratogens. Overall compliance was maintained after 3 months of follow-up and throughout therapy.

Signal Detection Based on Time to Onset Algorithm in Spontaneous Reporting System of China

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ABSTRACT

Introduction: The method of time-to-onset (TTO) has been proposed to overcome the drawbacks of traditional disproportionality analyses (DPAs), and it has been used for detecting safety signals of vaccines and some non-vaccine products in spontaneous reporting systems (SRSs). However, there is no consensus on its superiority over DPAs. Further, it is still not clear whether this novel approach can be generalized to the entire national SRS database.

Objective: The purpose of this study was to generalize the TTO method to the Chinese SRS and to identify suitable parameters for its optimal performance.

Methods: Reports submitted to the national SRS of China in 2014 were used as the data source for analysis. We evaluated the performance of TTO by using product labels as proxies for the gold standard. A series of values of significance level and time windows were explored to identify the most suitable parameters for TTO based on Youden's index, a statistic that summarizes the performance of a diagnostic test. Additionally, we compared TTO with traditional DPAs and explored the characteristics of signals detected by these methods.

Results: Compared with DPAs, TTO had a lower sensitivity, but higher specificity and positive predictive value. At a significance level of 0.2 and no restrictions on time windows, TTO had the highest Youden's index. The kappa coefficients between TTO and DPAs were rather low, indicating poor agreement between the two methods. More than 30% of the true signals detected by TTO were not identified by DPAs. Furthermore, TTO needed more number of reports to be able to detect signals.

Conclusions: TTO can detect signals missed by traditional DPAs and could be an important complementary tool to the currently used DPAs in the SRS of China. We recommend a significance level of 0.2 and no restrictions on time windows for TTO.

Diverging Conclusions from the Same Meta-Analysis in Drug Safety: Source of Data (Primary versus Secondary) Takes a Toll

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ABSTRACT

Introduction: Meta-analyses of observational studies represent an important tool for assessing efficacy and safety in the pharmacoepidemiologic field. The data from the individual studies are either primary (i.e., collected through interviews or self-administered questionnaires) or secondary (i.e., collected from databases that were established for other purposes). So far, the origin of the data (primary vs. secondary) has not been systematically assessed as a source of heterogeneity in pharmacoepidemiologic meta-analyses.

Objective: The aim was to assess the impact of considering the source of exposure data as a criterion in sensitivity and subgroup analysis on the conclusions of drug safety meta-analyses.

Methods: We selected meta-analyses published between 2013 and 2015 in which the intake of frequently used over-the-counter medicines was either the main exposure or a concomitant treatment and the outcome had short latency and induction periods. We stratified the results by origin of data (primary vs. secondary) and compared the new results to those presented originally in the meta-analyses.

Results: We used four meta-analyses that fulfilled our criteria of inclusion. The results were selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: original estimate odds ratio (OR) = 1.71 [95% confidence interval (CI) 1.44–2.04], OR primary data = 1.19 (95% CI 0.90–1.58), OR secondary data = 1.81 (95% CI 1.50–2.17); proton pump inhibitors and cardiac events: original estimate hazard ratio (HR) = 1.35 (95% CI 1.18–1.54), HR primary data = 1.05 (95% CI 0.87–1.26), HR secondary data = 1.43 (95% CI 1.23–1.66); non-aspirin non-steroidal anti-inflammatory drugs and myocardial infarction: original estimate risk ratio (RR) = 1.08 (95% CI 0.95–1.22), RR primary data = 0.57 (95% CI 0.34–0.96), RR secondary data = 1.15 (95% CI 1.03–1.28); paracetamol during pregnancy and childhood asthma: original estimate OR = 1.32 (95% CI 1.14–1.52), OR primary data = 1.23 (95% CI 1.06–1.42), OR secondary data = 1.53 (95% CI 1.33–1.75).

Conclusions: The results after stratification are considerably modified. It is crucial to explore the origin of the data, either primary or secondary, as a source of heterogeneity in pharmacoepidemiologic meta-analyses to avoid misleading conclusions.

Causality Assessment in Pharmacovigilance: Still a Challenge

Ralph Edwards

ABSTRACT

Causality in pharmacovigilance is a difficult and time consuming exercise. This paper presents the challenges in determining causation by drug therapy. The first is that causation is complex and needs to be viewed from the context of the patient treated, rather than the drug product. Multiple causal vectors should be considered if we are to tackle the many issues involved in, for example, medication error and the many other factors that lead to bad outcomes from therapy, including failure to recognise known risk factors. The aim of pharmacovigilance is not only a bureaucratic exercise in public health norms, but is mainly concerned with small minorities of statistical outliers—and even individuals—whose experiences from harms may together form messages about causation that will prevent further at-risk patients from exposure, or at least assist with earlier recognition of drug-related harm and better management of such harm. This requires more time, more data, more analysis and more patient and clinical involvement in reporting useful clinical detail. The paradigm shift back towards gathering more case data relating to possible causation can be selective and would not be just retrogressive, nor necessarily too costly. Greater transparency of hypotheses and availability of anonymised case data will enrol more expertise into evaluations and hypothesis testing, and the provision of more complete and useful information should reduce clinical burdens from bad patient outcomes as well as their overall costs to society.

Anti-Angiogenic Tyrosine Kinase Inhibitors and Reversible Posterior Leukoencephalopathy Syndrome: Could Hypomagnesaemia Be the Trigger

Rashmi R. Shah

ABSTRACT

Reversible posterior leukoencephalopathy syndrome (RPLS), also known frequently as posterior reversible encephalopathy syndrome (PRES), is a characteristic acute neuro-radiology syndrome with clinical presentation that typically includes acute hypertension, seizures and other neurological symptoms and signs. Many patients with RPLS have (a history of) pre-existing hypertension and in receipt of diuretics. It is being diagnosed more frequently and in association with an increasing number of morbidities and medications. Drugs most frequently implicated are immunosuppressant drugs and anticancer agents, including a number of anti-angiogenic tyrosine kinase inhibitors (TKIs). Hypomagnesaemia is a frequent finding at presentation in RPLS patients, which is known to lead to or aggravate hypertension. Pre-eclampsia, a variant of RPLS, responds effectively to intravenous magnesium. Cyclosporin, tacrolimus and some TKIs that induce RPLS are also known to give rise to both hypertension and hypomagnesaemia. This raises an interesting hypothesis that hypomagnesaemia may play a contributory role in triggering RPLS in some patients by acutely raising the blood pressure further. Additional systematic studies are required to test this hypothesis. If the hypothesis is confirmed, hypomagnesaemia offers an effective target for risk mitigation and prevention of RPLS in patients identified at risk.

Sensitivity of the UK Clinical Practice Research Datalink to Detect Neurodevelopmental Effects of Medicine Exposure in Utero: Comparative Analysis of an Antiepileptic Drug-Exposed Cohort

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ABSTRACT

Introduction: Electronic healthcare data have several advantages over prospective observational studies, but the sensitivity of data on neurodevelopmental outcomes and its comparability with data generated through other methodologies is unknown.

Objectives: The objectives of this study were to determine whether data from the UK Clinical Practice Research Datalink (CPRD) produces similar risk estimates to a prospective cohort study in relation to the risk of neurodevelopmental disorders (NDDs) following prenatal antiepileptic drug (AED) exposure.

Methods: A cohort of mother–child pairs of women with epilepsy (WWE) was identified in the CPRD and matched to a cohort without epilepsy. The study period ran from 1 January 2000 to 31 March 2007 and children were required to be in the CPRD at age 6 years. AED exposure during pregnancy was determined from prescription data and children with an NDD diagnosis by 6 years were identified from Read clinical codes. The prevalence and risk of NDDs was calculated for mother–child pairs in WWE stratified by AED regimen and for those without epilepsy. Comparisons were made with the results of the prospective Liverpool and Manchester Neurodevelopment Group study which completed assessment on 201 WWE and 214 without epilepsy at age 6 years.

Results: In the CPRD, 1018 mother–child pairs to WWE and 6048 to women without epilepsy were identified. The CPRD identified a lower prevalence of NDDs than the prospective study. In both studies, NDDs were more frequently reported in children of WWE than women without epilepsy, although the CPRD risk estimate was lower (2.16 vs. 0.96%, $p < 0.001$ and 7.46 vs. 1.87%, $p = 0.0128$). NDD prevalence differed across AED regimens but the CPRD data did not replicate the significantly higher risk of NDDs following in utero monotherapy valproate exposure (adjusted odds ratio [ORadj] 2.02, 95% confidence interval [CI] 0.52–7.86) observed in the prospective study (ORadj 6.05, 95% CI 1.65–24.53).

Conclusion: It was possible to identify NDDs in the CPRD; however, the CPRD appears to under-record these outcomes. Larger studies are required to investigate further.

Validation of New Signal Detection Methods for Web Query Log Data Compared to Signal Detection Algorithms Used With FAERS

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ABSTRACT

Introduction: Post-marketing drug surveillance is largely based on signals found in spontaneous reports from patients and healthcare providers. Rare adverse drug reactions and adverse events (AEs) that may develop after long-term exposure to a drug or from drug interactions may be missed. The US FDA and others have proposed that web-based data could be mined as a resource to detect latent signals associated with adverse drug reactions.

Methods: Recently, a web-based search query method called a query log reaction score (QLRS) was developed to detect whether AEs associated with certain drugs could be found from search engine query data. In this study, we compare the performance of two other algorithms, the proportional query ratio (PQR) and the proportional query rate ratio (Q-PRR) against that of two reference signal-detection algorithms (SDAs) commonly used with the FDA AE Reporting System (FAERS) database.

Results: In summary, the web query methods have moderate sensitivity (80%) in detecting signals in web query data compared with reference SDAs in FAERS when the web query data are filtered, but the query metrics generate many false-positives and have low specificity compared with reference SDAs in FAERS.

Conclusion: Future research is needed to find better refinements of query data and/or the metrics to improve the specificity of these web query log algorithms.

Feasibility and Educational Value of a Student-Run Pharmacovigilance Programme: A Prospective Cohort Study

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ABSTRACT

Introduction: Pharmacovigilance, the monitoring of drug safety after marketing approval, highly depends on the adequate reporting of adverse drug reactions (ADRs). To improve pharmacovigilance awareness and future ADR reporting among medical students, we developed and evaluated a student-run pharmacovigilance programme.

Methods: In this project, teams of medical students (first- to fifth-year) assessed real ADR reports, as submitted to the national pharmacovigilance centre. After assessment of causality, including identification of a potential pharmacological explanation for the ADR, the students wrote a personalized feedback letter to the reporter, as well as a summary for the European Medicines Agency (EMA) and World Health Organization (WHO) pharmacovigilance databases. This student assessment was then verified and evaluated by staff from The Netherlands Pharmacovigilance Centre Lareb (Lareb), using an e-questionnaire. Student attitudes, intentions, skills, and knowledge of ADR reporting were evaluated using the e-questionnaire, before and after participation in the programme.

Results: From May 2014 to January 2015, a total of 43 students assessed 100 different ADR reports selected by Lareb staff (n = 3). Student assessments were rated as useful (93%), scientifically substantiated (90%), accurate (92%), and complete (92%), and, on average, did not cost Lareb staff extra time. Medical students were positive about ADR reporting, and their awareness of ADR reporting increased significantly following participation in the programme ($p < 0.05$). After participation in the programme, the students intended to report serious ADRs in their future practice, and their knowledge of pharmacovigilance and ADR reporting showed they had a high overall level of pharmacological understanding.

Conclusion: The student-run pharmacovigilance programme is a win–win venture. It offers students a valuable ‘pharmacovigilance experience’, creates awareness in future doctors, and has the potential to increase pharmacovigilance skills and knowledge.

Evaluation of Potentially Drug-Related Patient-Reported Common Symptoms Assessed During Clinical Medication Reviews: A Cross-Sectional Observational Study

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ABSTRACT

Introduction: Healthcare professionals tend to consider common non-alarming drug-related symptoms to be of little clinical relevance. However, such symptoms can have a substantial impact on the individual patient. Insight into patient-reported symptoms could aid pharmacists to identify improvements in medication treatment, for instance in the patient interview at the start of a clinical medication review (CMR).

Objective: The objectives of this study were to describe the numbers and types of patient-reported symptoms assessed during a CMR and to elucidate their potential association with the drugs in use.

Methods: This observational study was performed using data from a clinical trial on patient-reported outcomes of CMRs. Patients taking at least five drugs and who were eligible for a CMR were selected by 15 community pharmacies. Patients were asked to fill in a structured instrument, the Patient Reported Outcome Measure, Inquiry into Side Effects (PROMISE). Among other domains, this instrument offers a list of 22 symptom categories to report symptoms and their relationship with the drugs in use. The results of the PROMISE instrument together with information on patients' actual drug use were available for analysis. Besides descriptive analysis, associations with side effects as listed in the summary of product characteristics (SPC) of the drugs in use were assessed with logistic regression analysis.

Results: Of the 180 patients included, 168 patients (93.3%) reported at least one symptom via the PROMISE instrument, which could be discussed with the pharmacist during the patient interview. In total, the patients reported 1102 symptoms in 22 symptom categories. Of these patients, 101 (56.1%) assumed that at one or more of the symptoms experienced were related to the drugs in use and 107 (59.4%) reported at least one symptom that corresponded to a 'very common' side effect listed in the SPC of a drug in use. Each additional drug in use with a specific symptom listed as a 'very common' side effect in its SPC statistically significantly increased the probability of a patient reporting the symptoms of 'dry mouth/thirst, mouth complaints', 'constipation', 'diarrhoea' and 'sweating'.

Conclusion: Many patient-reported symptoms and symptoms potentially related to drugs in use were identified by administering the PROMISE instrument to users of at least five drugs being taking long-term. This information can be used in CMRs to improve patients' drug therapy.

Post-Marketing Regulation of Medicines Withdrawn from the Market Because of Drug-Attributed Deaths: An Analysis of Justification

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ABSTRACT

Introduction: Several medicinal products have been withdrawn from the market because of drug-attributed deaths. However, there has been no investigation of whether such withdrawals were justified, and the extent to which confirmatory studies are used to investigate drug-adverse event relationships when deaths are reported is uncertain. We documented medicinal products withdrawn from the market because of drug-attributed deaths, identified confirmatory studies investigating the drug-adverse event relationships, examined whether withdrawals of medicinal products because of drug-attributed deaths after marketing were justified based on a mechanistic analysis, and examined the trends over time.

Methods: We searched electronic and non-electronic sources to identify medicinal products that were withdrawn because of drug-attributed deaths. We used a previously published algorithm to examine whether the withdrawals of products were justified. We then searched PubMed and Google Scholar to identify studies investigating the drug-adverse event relationships, used the Oxford Centre for Evidence-Based Medicine criteria to document the levels of evidence, and assessed whether the evidence of an association was confirmed.

Results: We included 83 medicinal products. The reasons for withdrawal appeared to have been justified in 80 cases (96%). The median interval between the first reported adverse reaction that was related to the cause of death and the first reported death was 1 year (interquartile range = 1–3); products were withdrawn sooner when the interval between the first reported relevant adverse reaction and the first death was shorter. Confirmatory studies were conducted in 57 instances (69%), and there was evidence of an association in 52 cases (63%). Four products (5%) were re-introduced after initial withdrawal.

Conclusion: Regulatory authorities have been justified in making withdrawal decisions when deaths have been attributed to medicinal products, using the precautionary principle when alternative decisions could have been made. Medicinal products are likely to be quickly withdrawn from the market when there is a short interval to the first reported deaths. The use of an algorithm such as we have used in this study could help to expedite the process of decision making.

Factors Influencing the Use of a Mobile App for Reporting Adverse Drug Reactions and Receiving Safety Information: A Qualitative Study

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ABSTRACT

Introduction: A mobile app may increase the reporting of adverse drug reactions (ADRs) and improve the communication of new drug safety information. Factors that influence the use of an app for such two-way risk communication need to be considered at the development stage.

Objective: Our aim was to reveal the factors that may influence healthcare professionals (HCPs) and patients to use an app for two-way risk communication.

Methods: Focus group discussions and face-to-face interviews were conducted in the Netherlands, Spain and the UK. Patients with type 2 diabetes mellitus, patients with a rare disease or their caregivers and adolescents with health conditions were eligible to participate. HCPs included pharmacists, paediatricians, general practitioners, internists, practice nurses and professionals caring for patients with a rare disease. Patients and HCPs were recruited through various channels. The recorded discussions and interviews were transcribed verbatim. The dataset was analysed using thematic analysis and arranged according to the Unified Theory of Acceptance and Use of Technology.

Results: Seven focus group discussions and 13 interviews were conducted. In total, 21 HCPs and 50 patients participated. Identified factors that may influence the use of the app were the type of feedback given on reported ADRs, how ADR reports are stored and the type of drug news. Also mentioned were other functions of the app, ease of use, type of language, the source of safety information provided through the app, security of the app, layout, the operating systems on which the app can be used and the costs.

Conclusions: Further research is needed to assess associations between user characteristics and the direction (positive or negative) of the factors potentially influencing app use.

Adverse Drug Event Causality Analysis (ADECA): A Process for Evaluating Evidence and Assigning Drugs to Risk Categories for Sudden Death

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ABSTRACT

Growing evidence indicates that many drugs have the ability to cause a potentially lethal cardiac arrhythmia, torsades de pointes (TdP). This necessitates the development of a compilation of drugs that have this potential toxicity. Such a list is helpful in identifying the etiology of TdP in patients taking multiple drugs and assists decision making by those caring for patients at high risk of TdP. The Arizona Center for Education and Research on Therapeutics (AZCERT) has developed a process to standardize the identification of drugs and place them in risk categories for their clinical ability to cause TdP and QT prolongation. AZCERT's Adverse Drug Event Causality Analysis (ADECA) utilizes 16 types of data drawn from four sources to compile an open-source knowledge base, QTdrugs, which is maintained on the CredibleMeds.org website. Because the evidence for most drugs is incomplete, the ADECA process is used to place drugs into one of three categories that represent different levels of certainty: known TdP risk, possible TdP risk, and conditional TdP risk. Each category has strict evidentiary requirements for clinical evidence of TdP and/or QT prolongation. These are described in this paper. Because evidence can evolve over time, the ADECA process includes the continuous gathering and analysis of newly emerging evidence to revise the lists. The QTdrugs lists have proven to be a valued, readily available, commercial influence-free resource for healthcare providers, patients, researchers, and authors of consensus guidelines for the safe use of medicines.

Pharmacovigilance of Regenerative Medicine under the Amended Pharmaceutical Affairs Act in Japan

Yasuko Inokuma

ABSTRACT

Two Japanese regulatory agencies, the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency announced the implementation of a new review system called 'Conditional Approval,' specifically for the emerging field of regenerative medicine, in an amendment to the Pharmaceutical Affairs Act in 2014. Regenerative medicine was regulated in the category of 'Medical Devices' prior to the amendment and was not covered by the Relief Service, a system that provides financial aid to people who have experienced an adverse drug reaction and developed serious side effects as a result. Through the amendment, regenerative medicine is defined as a new category and is covered by the Relief Service under the amended Pharmaceutical Affairs Act, called the 'Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics' (PMD Act). This amendment allows the use of Relief Service data for pharmacovigilance activities, making the Relief Service the third adverse drug reaction reporting route in addition to the existing reporting routes from marketing authorization holders and healthcare providers. For optimum incorporation and use of this Relief Service data, earlier access should be allowed even before the reports from the Pharmaceuticals and Medical Devices Agency to the Ministry of Health, Labour and Welfare are finalized, which is mandatory under the current PMD Act.

Evaluation of 'SAEFVIC', A Pharmacovigilance Surveillance Scheme for the Spontaneous Reporting of Adverse Events Following Immunisation in Victoria, Australia

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ABSTRACT

Introduction: Australia is traditionally an early adopter of vaccines, therefore comprehensive and effective post-licensure vaccine pharmacovigilance is critical to maintain confidence in immunisation, both nationally and internationally. With adverse event following immunisation (AEFI) surveillance the responsibility of Australian jurisdictions, Victoria operates an enhanced passive AEFI surveillance system integrated with clinical services, called 'SAEFVIC' (Surveillance of Adverse Events Following Vaccination In the Community).

Objective: The aim of this study was to evaluate Victoria's current AEFI surveillance system 'SAEFVIC' and inform ongoing quality improvement of vaccine pharmacovigilance in Victoria and Australia.

Methods: We conducted a retrospective structured desktop evaluation of AEFI reporting received by SAEFVIC from 2007 to 2014, to evaluate the system according to its stated objectives, i.e. to improve AEFI reporting; provide AEFI signal detection; and to maintain consumer confidence in vaccination.

Results: AEFI reporting has tripled since SAEFVIC commenced (incidence risk ratio [IRR] 3.04, 95% confidence interval [CI] 2.35–3.93), raising Victoria to be the lead jurisdiction by AEFI reporting volume and to rank third by population reporting rate nationally. The largest increase was observed in children. Data were utilised to investigate potential signal events and inform vaccine policy. Signal detection required clinical suspicion by surveillance nurses, or prior vaccine-specific concerns. Subsequent vaccination post-AEFI was documented for 56.2% (95% CI 54.1–58.4) of reports, and the proportion of children due or overdue for vaccination was 2.3% higher for those reporting AEFI compared with the general population.

Conclusion: SAEFVIC has improved AEFI surveillance, facilitates signal investigation and validation, and supports consumer confidence in immunisation. Expansion of the system nationally has the potential to improve capacity and capability of vaccine pharmacovigilance, particularly through data consistency and jurisdictional comparability in Australia.

Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals

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ABSTRACT

Introduction: An important goal in drug regulation understands serious safety issues with new drugs as soon as possible. Achieving this goal requires us to understand whether information provided during the Food and Drug Administration (FDA) drug review can predict serious safety issues that are usually identified after the product is approved. However, research on this topic remains understudied. In this paper, we examine whether any pre-marketing drug characteristics are associated with serious post-marketing safety actions.

Methods: We study this question using an internal FDA database containing every new small molecule drug submitted to the FDA's Center for Drug Evaluation and Research (CDER) on or after November 21, 1997, and approved and commercially launched before December 31, 2009. Serious post-marketing safety actions include whether these drugs ever experienced either a post-marketing boxed warning or a withdrawal from the market due to safety concerns. A random effects logistic regression model was used to test whether any pre-marketing characteristics were associated with either post-marketing safety action.

Results: A total of 219 new molecular entities were analyzed. Among these drugs, 11 experienced a safety withdrawal and 30 received boxed warnings by July 31, 2016. Contrary to prevailing hypotheses, we find that neither clinical trial sample sizes nor review time windows are associated with the addition of a post-marketing boxed warning or safety withdrawal. However, we do find that new drugs approved with either a boxed warning or priority review are more likely to experience post-marketing boxed warnings. Furthermore, drugs approved with boxed warnings tend to receive post-marketing boxed warnings resulting from new safety information that are unrelated to the original warning. Drugs approved with a boxed warning are 3.88 times more likely to receive a post-marketing boxed warning, while drugs approved with a priority review are 3.51 times more likely to receive a post-marketing boxed warning.

Conclusion: Although drugs approved with a boxed warning or priority review are more likely to experience serious post-marketing safety events, other information provided during the FDA drug review that is easy to quantify is generally not associated with post-marketing safety events. It appears that these post-marketing events are not discernible during a pre-marketing review and therefore might not be avoidable using current review data.

The Risk of Ischemic Cardio- and Cerebrovascular Events Associated with Oxycodone–Naloxone and Other Extended-Release High-Potency Opioids: A Nested Case–Control Study

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ABSTRACT

Introduction: In Germany, an extended-release (ER) combination of the high-potency opioid (HPO) oxycodone and the antagonist naloxone was approved in 2006. In recent years, the cardio- and cerebrovascular safety of opioid antagonists and of opioids themselves has been discussed.

Objectives: The objective of this study was to estimate the risk of major ischemic cardio- and cerebrovascular events in patients receiving ER oxycodone–naloxone compared with those receiving other ER HPOs.

Methods: We used the German Pharmacoepidemiological Research Database (GePaRD) to conduct a nested case–control study (2006–2011) within a cohort of ER HPO users. Cases were defined as patients hospitalized for acute myocardial infarction (MI) or ischemic stroke (IS). For each case, up to ten controls were selected by risk-set sampling. Using conditional logistic regression, confounder-adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were obtained for the risk of MI/IS associated with (1) current HPO treatment, (2) recent discontinuation, or (3) recent switch of HPO therapy compared with past treatment.

Results: In 309,936 ER HPO users, 12,384 MI/IS events were detected, resulting in a crude incidence rate of 19.48 (95% CI 19.14–19.82) per 1000 person years. A small but significantly elevated aOR was found for morphine (1.12; 95% CI 1.04–1.22) but not for oxycodone–naloxone. Recent discontinuation and recent switch of any ER HPO also had a significant impact on the outcome (aOR 1.12; 95% CI 1.04–1.21 and 1.25; 95% CI 1.03–1.52, respectively).

Conclusions: Our study does not indicate an association between oxycodone–naloxone and ischemic cardio- or cerebrovascular events. However, our findings do suggest that every change in ER HPO therapy should be conducted with caution.

A Survey on Pharmacovigilance Activities in ASEAN and Selected Non-ASEAN Countries, and the Use of Quantitative Signal Detection Algorithms

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ABSTRACT

Introduction: Most Countries have pharmacovigilance (PV) systems in place to monitor the safe use of health products. The process involves the detection and assessment of safety issues from various sources of information, communicating the risk to stakeholders and taking other relevant risk minimization measures.

Objectives: This study aimed to assess the PV status in Association of Southeast Asian Nation (ASEAN) countries, sources for postmarket safety monitoring, methods used for signal detection and the need for a quantitative signal detection algorithm (QSDA). Comparisons were conducted with centres outside ASEAN.

Methods: A questionnaire was sent to all PV centres in ASEAN countries, as well as seven other countries, from November 2015 to June 2016. The questionnaire was designed to collect information on the status of PV, with a focus on the use of a QSDA.

Results: Data were collected from nine ASEAN countries and seven other countries. PV activities were conducted in all these countries, which were at different stages of development. In terms of adverse drug reaction (ADR) reports, the average number received per year ranged from 3 to 50,000 reports for ASEAN countries and from 7000 to 1,103,200 for non-ASEAN countries. Thirty-three percent of ASEAN countries utilized statistical methods to help detect signals from ADR reports compared with 100% in the other non-ASEAN countries. Eighty percent agreed that the development of a QSDA would help in drug signal detection. The main limitation identified was the lack of knowledge and/or lack of resources.

Conclusion: Spontaneous ADR reports from healthcare professionals remains the most frequently used source for safety monitoring. The traditional method of case-by-case review of ADR reports prevailed for signal detection in ASEAN countries. As the reports continue to grow, the development of a QSDA would be useful in helping detect safety signals.

Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study

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ABSTRACT

Introduction: The US Food and Drug Administration uses drug safety communications (DSCs) to release emerging information regarding post-market safety issues, but it is unclear the extent of awareness by patients and providers of these communications and their specific recommendations.

Objective: We conducted semi-structured interviews with patients and physicians to evaluate their awareness and understanding of emerging drug safety information related to two sleep aids: zolpidem or eszopiclone.

Methods: We conducted interviews with 40 patients and ten physicians recruited from a combination of insurer claims databases and online sources. We evaluated (1) sources of drug safety information; (2) discussions between patients and physicians about the two medications; (3) their knowledge of the DSC; and (4) preferences for learning about future drug safety information. Interviews were transcribed and analyzed thematically.

Results: Patients cited their physicians, pharmacy inserts, and the Internet as sources of drug safety information. Physicians often referred to medical journals and online medical sources. Most patients reported being aware of information contained in the DSC summaries they were read. Almost all patients and physicians reported discussing side effects during patient-provider conversations, but almost no patients mentioned that physicians had communicated with them key messaging from the DSCs at issue: the risk of next-morning impairment with zolpidem and the lower recommended initial dose for women.

Conclusions: Some risks of medications are effectively communicated to patients and physicians; however, there is still a noticeable gap between information issued by the Food and Drug Administration and patient and physician awareness of this knowledge, as well as patients' decisions to act on this information. Disseminators of emerging drug safety information should explore ways of providing user-friendly resources to patients and healthcare professionals that can update them on new risks in a timely manner.

Summarising the Evidence for Drug Safety: A Methodological Discussion of Different Meta-Analysis Approaches

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ABSTRACT

Evidence on drug safety obtained from randomised clinical trials is very limited due to, among other reasons, their relatively small sample size. Hence, combining the results of available studies can prove particularly useful. This paper reviews the different data sources for summarising drug safety outcomes, according to study design, publication of data, and origin of the information. It then discusses the various types of overviews that can be used in the study of treatment harms, focusing on meta-analyses of aggregate data and meta-analyses of individual patient data, with their advantages and drawbacks, such as publication bias and heterogeneity. Although the different approaches available for combining the results are of great utility in assessing treatment harms, none of them is free from limitations. Therefore, it might be appropriate to perform an analysis of sensitivity to assess whether the results are sensitive to the technique that has been used.

Targeting Interleukin-5 or Interleukin-5Rα: Safety Considerations

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ABSTRACT

Asthma is a highly prevalent chronic disease of the airways; approximately 10% of patients with asthma will experience a severe form of the disease. New understanding of the pathogenesis of asthma has enabled the development of novel drugs and provided hope for patients with asthma. Interleukin (IL)-5 and IL-5 receptor subunit α (IL-5-Rα) plays a crucial role in the development, maturation, and operation of eosinophils so were the first important therapeutic target of these new drugs. While the results of early clinical trials of these drugs were not promising, results improved once researchers discovered the drugs worked best in patients with high eosinophil levels. Patients treated with both anti-IL-5 and IL-5-Rα experienced significant decreases in exacerbations. Trials have also demonstrated promising safety profiles; adverse events have been few and frequently only observed with placebo or considered unrelated to the study drug. The positive efficacy and safety profiles of these drugs has led to trials with interesting results in other diseases that are also secondary to the action of eosinophils: Churg–Strauss syndrome, hypereosinophilic syndrome, nasal polyposis, chronic obstructive pulmonary disease, atopic dermatitis, and esophagitis. In this review, we explore the main clinical trials of anti-IL-5 and IL-5-Rα, both in asthma and in other pathologies, with particular reference to the interesting safety and efficacy results.

Using Probabilistic Record Linkage of Structured and Unstructured Data to Identify Duplicate Cases in Spontaneous Adverse Event Reporting Systems

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ABSTRACT

Introduction: Duplicate case reports in spontaneous adverse event reporting systems pose a challenge for medical reviewers to efficiently perform individual and aggregate safety analyses. Duplicate cases can bias data mining by generating spurious signals of disproportional reporting of product-adverse event pairs.

Objective: We have developed a probabilistic record linkage algorithm for identifying duplicate cases in the US Vaccine Adverse Event Reporting System (VAERS) and the US Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: In addition to using structured field data, the algorithm incorporates the non-structured narrative text of adverse event reports by examining clinical and temporal information extracted by the Event-based Text-mining of Health Electronic Records system, a natural language processing tool. The final component of the algorithm is a novel duplicate confidence value that is calculated by a rule-based empirical approach that looks for similarities in a number of criteria between two case reports.

Results: For VAERS, the algorithm identified 77% of known duplicate pairs with a precision (or positive predictive value) of 95%. For FAERS, it identified 13% of known duplicate pairs with a precision of 100%. The textual information did not improve the algorithm's automated classification for VAERS or FAERS. The empirical duplicate confidence value increased performance on both VAERS and FAERS, mainly by reducing the occurrence of false-positives.

Conclusions: The algorithm was shown to be effective at identifying pre-linked duplicate VAERS reports. The narrative text was not shown to be a key component in the automated detection evaluation; however, it is essential for supporting the semi-automated approach that is likely to be deployed at the Food and Drug Administration, where medical reviewers will perform some manual review of the most highly ranked reports identified by the algorithm.

Drospirenone-Containing Oral Contraceptive Pills and the Risk of Venous Thromboembolism: An Assessment of Risk in First-Time Users and Restarters

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ABSTRACT

Introduction: The effects of drospirenone-containing combined oral contraceptives (COCs) on the risk of venous thromboembolism (VTE) remain controversial due to the challenge in distinguishing between first-time users and restarters, and their different underlying VTE risks, in healthcare databases.

Objectives: The aim of this study was to describe the challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs in a healthcare database and assess the risk among first-time users and restarters.

Methods: We used data from the Clinical Practice Research Datalink to construct two cohorts. The first-time user cohort included all women aged 16–45 years who received a first ever prescription of drospirenone- or levonorgestrel-containing COCs between May 2002 and March 2015. The restarter cohort included those who were restarting a COC after a period of non-use of ≥6 months. Cox proportional hazards models adjusted for high dimensional propensity scores were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The final cohorts included 55,139 first-time users (3582 drospirenone and 51,557 levonorgestrel) and 162,959 restarters (23,191 drospirenone and 139,768 levonorgestrel). The adjusted HR of VTE associated with drospirenone versus levonorgestrel was 3.19 (95% CI 1.12–9.08) for first-time users and 1.96 (95% CI 1.12–3.41) for restarters.

Conclusions: We found an elevated risk of VTE associated with drospirenone-containing COCs in comparison with levonorgestrel-containing COCs in both cohorts. While left truncation of healthcare databases is a concern for the identification of first-time users, the use of a more explicit cohort of restarters suggests a doubling of VTE risk with drospirenone-containing COCs.

Adverse Drug Reaction-Related Hospitalizations in Elderly Australians: A Prospective Cross-Sectional Study in Two Tasmanian Hospitals

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ABSTRACT

Introduction: Adverse drug reactions (ADRs) have been commonly cited as a major cause of hospital admissions in older individuals. However, despite the apparent magnitude of this problem, there are limited prospective data on ADRs as a cause of hospitalization in elderly medical patients.

Objectives: The objective of this study was to evaluate the proportion, clinical characteristics, causality, severity, preventability, and outcome of ADR-related admissions in older patients admitted to two Tasmanian hospitals.

Methods: We conducted a prospective cross-sectional study at the Royal Hobart and Launceston General Hospitals in Tasmania, Australia. A convenience sample of patients, aged 65 years and older, undergoing unplanned overnight medical admissions was screened. ADR-related admissions were determined through expert consensus from detailed review of medical records and patient interviews. The causality, preventability and severity of each ADR-related admission were assessed.

Results: Of 1008 admissions, the proportion of potential ADR-related medical admissions was 18.9%. Most (88.5%) ADR-related admissions were considered preventable. Cardiovascular complaints (29.3%) represented the most common ADRs, followed by neuropsychiatric (20.0%) and renal and genitourinary disorders (15.2%). The most frequently implicated drug classes were diuretics (23.9%), agents acting on the renin angiotensin system (16.4%), β-blocking agents (7.1%), antidepressants (6.9%), and antithrombotic agents (6.9%). Application of the Naranjo algorithm found 5.8% definite, 70.1% probable, and 24.1% possible ADRs. ADR severity was rated moderate and severe in 97.9% and 2.1% of admissions, respectively. For most (93.2%) ADR-related admissions the ADR resolved and the patient recovered.

Conclusion: Hospitalization due to an ADR is a common occurrence in this older population. There is need for future studies to implement and evaluate interventions to reduce the risk of ADR-related admissions in elderly populations.

The Quality of Clinical Information in Adverse Drug Reaction Reports by Patients and Healthcare Professionals: A Retrospective Comparative Analysis

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ABSTRACT

Introduction: Clinical information is needed to assess the causal relationship between a drug and an adverse drug reaction (ADR) in a reliable way. Little is known about the level of relevant clinical information about the ADRs reported by patients.

Objective: The aim was to determine to what extent patients report relevant clinical information about an ADR compared with their healthcare professional.

Methods: A retrospective analysis of all ADR reports on the same case, i.e., cases with a report from both the patient and the patient's healthcare professional, selected from the database of the Dutch Pharmacovigilance Center Lareb, was conducted. The extent to which relevant clinical information was reported was assessed by trained pharmacovigilance assessors, using a structured tool. The following four domains were assessed: ADR, chronology, suspected drug, and patient characteristics. For each domain, the proportion of reported information in relation to information deemed relevant was calculated. An average score of all relevant domains was determined and categorized as poorly (≤45%), moderately (from 46 to 74%) or well (≥75%) reported. Data were analyzed using a paired sample t test and Wilcoxon signed rank test.

Results: A total of 197 cases were included. In 107 cases (54.3%), patients and healthcare professionals reported a similar level of clinical information. Statistical analysis demonstrated no overall differences between the groups ($p = 0.126$).

Conclusions: In a unique study of cases of ADRs reported by patients and healthcare professionals, we found that patients report clinical information at a similar level as their healthcare professional. For an optimal pharmacovigilance, both healthcare professionals and patient should be encouraged to report.

Impact of Safety-Related Regulations on Codeine Use in Children: A Quasi-Experimental Study Using Taiwan's National Health Insurance Research Database

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ABSTRACT

Introduction: Safety concerns regarding potential life-threatening adverse events associated with codeine have resulted in policy decisions to restrict its use in pediatrics. However, whether these drug safety communications have had an immediate and strong impact on codeine use remains in question.

Objective: We aimed to investigate the impact of the two implemented safety-related regulations (label changes and reimbursement regulations) on the use of codeine for upper respiratory infection (URI) or cough.

Methods: A quasi-experimental study was performed using Taiwan's National Health Insurance Research Database. Quarterly data of codeine prescription rates for URI/cough visits were reported, and an interrupted time series design was used to assess the impact of the safety regulations on the uses of codeine among children with URI/cough visits. Multivariable logistic regression models were used to explore patient and provider characteristics associated with the use of codeine.

Results: The safety-related regulations were associated with a significant reduction in codeine prescription rates of −4.24% (95% confidence interval [CI] −4.78 to −3.70), and the relative reduction compared with predicted rates based on preregulation projections was 60.4, 56.6, and 53.2% in the first, second, and third year after the regulations began, respectively. In the postregulation period, physicians specializing in otolaryngology (odds ratio [OR] 1.47, 95% CI 1.45–1.49), practicing in district hospitals (OR 6.84, 95% CI 5.82–8.04) or clinics (OR 6.50, 95% CI 5.54–7.62), and practicing in the least urbanized areas (OR 1.60, 95% CI 1.55–1.64) were more likely to prescribe codeine to children than their counterparts.

Conclusions: Our study provides a successful example of how to effectively reduce the codeine prescriptions in children in the 'real-world' settings, and highlights areas where future effort could be made to improve the safety use of codeine. Future research is warranted to explore whether there was a simultaneous decrease in the incidence rates of codeine-related adverse events following the safety-related regulations.

Patient Reporting in the EU: Analysis of EudraVigilance Data

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ABSTRACT

Introduction: New pharmacovigilance legislation was adopted in the EU in 2010 and became operational in July 2012. The legislation placed an obligation on all national competent authorities (NCAs) and marketing authorisation holders (MAHs) to record and report cases of suspected adverse drug reactions (ADRs) received from patients.

Objectives: This descriptive study aims to provide insight into patient reporting for the totality of the EU by querying the EudraVigilance (EV) database for the period of 3 years before the new pharmacovigilance legislation became operational and the 3 years after as well as comparing patient reports with those from healthcare professionals (HCPs) where feasible.

Methods: We queried the EV database for the following characteristics of patient and HCP reports: demographics (patient sex and age), seriousness, reported ADR terms, reported indications, number of ADRs per report, time to report an ADR, and most reported substances. Wherever feasible, direct comparisons between patient reports and HCP reports were performed using relative risks.

Results: The EV database contained a total of 53,130 patient reports in the 3 years preceding the legislation operation period and 113,371 in the 3 years after. Member states contributing the most patient reports to the EV database were the Netherlands, the UK, Germany, France and Italy. The results for indications and substances show that patients were more likely than HCPs to report for genitourinary, hormonal and reproductive indications. Patients reported more in general disorders and administration site conditions Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), whereas HCPs reported more Preferred Terms (PTs) belonging in the Investigations SOC. However, 13 of the 20 reactions most frequently reported by patients were also among the top 20 reactions reported by HCPs.

Conclusion: Patient reporting complemented reporting by HCPs. Patients were motivated to report ADRs, especially those that affected their quality of life. Sharing these results with NCAs and patient associations can inform training and awareness on patient reporting.

Species Adulteration in the Herbal Trade: Causes, Consequences and Mitigation

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ABSTRACT

The global economy of the international trade of herbal products has been increasing by 15% annually, with the raw material for most herbal products being sourced from South and Southeast Asian countries. In India, of the 8000 species of medicinal plants harvested from the wild, approximately 960 are in the active trade. With increasing international trade in herbal medicinal products, there is also increasing concern about the widespread adulteration and species admixtures in the raw herbal trade. The adverse consequences of such species adulteration on the health and safety of consumers have only recently begun to be recognised and documented. We provide a comprehensive review of the nature and magnitude of species adulteration in the raw herbal trade, and identify the underlying drivers that might lead to such adulteration. We also discuss the possible biological and chemical equivalence of species that are used as adulterants and substitutes, and the consequences thereof to consumer health and safety, and propose a framework for the development of a herbal trade authentication service that can help regulate the herbal trade market.

Adjuvanted (AS03) A/H1N1 2009 Pandemic Influenza Vaccines and Solid Organ Transplant Rejection: Systematic Signal Evaluation and Lessons Learnt

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ABSTRACT

Introduction: We investigated a signal of solid organ transplant (SOT) rejection after immunisation with (AS03) A/H1N1 2009 pandemic influenza vaccines.

Methods: Potential immunological mechanisms were reviewed and quantitative analyses were conducted. The feasibility of pharmacoepidemiological studies was explored.

Results: Overall results, including data from a pharmacoepidemiological study, support the safety of adjuvanted (AS03) pandemic influenza vaccination in SOT recipients. The regulatory commitment to evaluate the signal through a stepwise investigation was closed in 2014.

Conclusion: Lessons learned highlight the importance of investigating plausible biological mechanisms between vaccines and potentially associated adverse outcomes, and the importance of selecting appropriate study settings and designs for safety signal investigations.

Managing Cardiovascular Risk of Macrolides: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: It was postulated that antibiotics including macrolides could be used for the secondary prevention of coronary heart disease but recent studies showed that macrolides increase the cardiovascular risk. We aimed to review the evidence of cardiovascular risk associated with macrolides regarding duration of effect and risk factors; and to explore the potential effect of statins for the prevention of cardiovascular events as a result of macrolide use.

Methods: Several electronic databases (PubMed, EMBASE, Cochrane library) were searched to identify eligible studies. Observational studies and randomized controlled trials that investigated the association between macrolides and cardiovascular events in adults aged ≥18 years were included. A meta-analysis was conducted to investigate the short- and long-term risks of cardiovascular mortality, myocardial infarction, arrhythmia, and stroke. Methodological quality was assessed by the Newcastle-Ottawa scale and the Cochrane Collaboration's tool. The body of evidence was evaluated by the Grading of Recommendations Assessment, Development, and Evaluation guidelines.

Results: Observational studies were found to have a short-term risk of cardiovascular outcomes including cardiovascular mortality, myocardial infarction, and arrhythmia associated with macrolides but no risk was found in randomized controlled trials. However, no association for long-term risk (ranging from >30 days to >3 years) was observed in observational studies or randomized controlled trials.

Limitations: The included studies reported different units of denominators for absolute risk and used different outcome definitions, which might increase the heterogeneity.

Conclusions: More studies are required to investigate the short-term cardiovascular outcomes associated with different types of macrolides. Future studies are warranted to evaluate the effect of statins for preventing excess acute cardiovascular events associated with clarithromycin or other macrolides.

Antipsychotic Prescribing to Patients Diagnosed with Dementia Without a Diagnosis of Psychosis in the Context of National Guidance and Drug Safety Warnings: Longitudinal Study in UK General Practice

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ABSTRACT

Introduction: Policy interventions to address inappropriate prescribing of antipsychotic drugs to older people diagnosed with dementia are commonplace. In the UK, warnings were issued by the Medicines Healthcare products Regulatory Agency in 2004, 2009 and 2012 and the National Institute for Health and Care Excellence guidance was published in 2006. It is important to evaluate the impact of such interventions.

Methods: We analysed routinely collected primary-care data from 111,346 patients attending one of 689 general practices contributing to the Clinical Practice Research Datalink to describe the temporal changes in the prescribing of antipsychotic drugs to patients aged 65 years or over diagnosed with dementia without a concomitant psychosis diagnosis from 2001 to 2014 using an interrupted time series and a before-and-after design. Logistic regression methods were used to quantify the impact of patient and practice level variables on prescribing prevalence.

Results: Prescribing of first-generation antipsychotic drugs reduced from 8.9% in 2001 to 1.4% in 2014 (prevalence ratio 2014/2001 adjusted for age, sex and clustering within practices (0.14, 95% confidence interval 0.12–0.16), whereas there was little change for second-generation antipsychotic drugs (1.01, confidence interval 0.94–1.17). Between 2004 and 2012, several policy interventions coincided with a pattern of ups and downs, whereas the 2006 National Institute for Health and Care Excellence guidance was followed by a gradual longer term reduction. Since 2013, the decreasing trend in second-generation antipsychotic drug prescribing has plateaued largely driven by the increasing prescribing of risperidone.

Conclusions: Increased surveillance and evaluation of drug safety warnings and guidance are needed to improve the impact of future interventions.

Detecting Signals of Disproportionate Reporting from Singapore's Spontaneous Adverse Event Reporting System: An Application of the Sequential Probability Ratio Test

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ABSTRACT

Introduction: The ability to detect safety concerns from spontaneous adverse drug reaction reports in a timely and efficient manner remains important in public health.

Objective: This paper explores the behaviour of the Sequential Probability Ratio Test (SPRT) and ability to detect signals of disproportionate reporting (SDRs) in the Singapore context.

Methods: We used SPRT with a combination of two hypothesised relative risks (hRRs) of 2 and 4.1 to detect signals of both common and rare adverse events in our small database. We compared SPRT with other methods in terms of number of signals detected and whether labelled adverse drug reactions were detected or the reaction terms were considered serious. The other methods used were reporting odds ratio (ROR), Bayesian Confidence Propagation Neural Network (BCPNN) and Gamma Poisson Shrinker (GPS).

Results: The SPRT produced 2187 signals in common with all methods, 268 unique signals, and 70 signals in common with at least one other method, and did not produce signals in 178 cases where two other methods detected them, and there were 403 signals unique to one of the other methods. In terms of sensitivity, ROR performed better than other methods, but the SPRT method found more new signals. The performances of the methods were similar for negative predictive value and specificity.

Conclusions: Using a combination of hRRs for SPRT could be a useful screening tool for regulatory agencies, and more detailed investigation of the medical utility of the system is merited.

Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences

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ABSTRACT

Introduction: National competent authorities (NCAs) for medicines coordinate communication relating to the safety of medicines in Europe. The effectiveness of current communication practices has been questioned, particularly with regard to reaching general practitioners (GPs).

Objective: The aim of this study was to assess current European NCA safety communication practices and to investigate European GPs' awareness of and preferences for safety communications on medicines.

Methods: Web-based surveys were distributed among European NCAs and healthcare professionals (HCPs). The survey among regulators was emailed to a representative of each of the 27 European countries participating in the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. HCPs from nine European countries (Denmark, Spain, Croatia, Ireland, Italy, The Netherlands, Norway, Sweden, and the UK) were asked about their preferences through a link to the survey on websites, in newsletters, and/or in a direct email. From this survey, data from GPs were used and descriptive analyses were conducted.

Results: Current NCA practices were reported for 26 countries. In 23 countries (88%), NCAs published direct healthcare professional communications (DHPCs, i.e. urgent communication letters for serious safety issues) on their website in addition to distribution to individual HCPs. Educational materials were available on the NCA's website in 10 countries (40%), and 21 NCAs (81%) indicated they had their own bulletin/newsletter, which is often presented on the NCA's website (15 countries; 60%). More than 90% of the 1766 GPs who completed the survey were aware of DHPCs. The most preferred senders of safety information were NCAs and professional bodies, while the preferred channels for keeping up to date with safety information were medicines reference books and clinical guidelines. GPs found the repetition of safety issues useful (range of 80% in the UK to 97% in Italy). Preference for an electronic copy rather than a hardcopy varied per country (36% in Sweden to 72% in Spain).

Conclusions: NCAs use similar methods for safety communications on medicines. Most GPs were aware of urgent communications and preferred similar senders of safety communications; however, their preferences towards the format differed per country.

People's Understanding of Verbal Risk Descriptors in Patient Information Leaflets: A Cross-Sectional National Survey of 18- to 65-Year-Olds in England

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ABSTRACT

Introduction: Evidence suggests the current verbal risk descriptors used to communicate side effect risk in patient information leaflets (PILs) are overestimated.

Objectives: The aim was to establish how people understand the verbal risk descriptors recommended for use in PILs by the European Commission (EC), and alternative verbal risk descriptors, in the context of mild and severe side effects.

Methods: A cross-sectional online survey was carried out by a market research company recruiting participants aged between 18 and 65 years living in England. Data were collected between 18 March and 1 April 2016. Participants were given a hypothetical scenario regarding the risk of mild or severe medication side effects and asked to estimate how many out of 10,000 people would be affected for each of the verbal risk descriptors being tested.

Results: A total of 1003 participants were included in the final sample. The risks conveyed by the EC recommended verbal risk descriptors were greatly overestimated by participants. Two distinct distributions were apparent for participant estimates of side effect risks: those for 'high risk' verbal descriptors (e.g. 'common', 'likely', 'high chance') and those for 'low risk' verbal descriptors (e.g. 'uncommon', 'unlikely', 'low chance'). Within these two groups, the distributions were near to identical regardless of what adverb (e.g. very, high, fair) or adjective (e.g. common, likely, chance) was used. The EC recommended verbal risk descriptors were more likely to be understood in accordance with their intended meanings when describing severe side effects. Very few demographic or psychological factors were consistently associated with how well participants understood the EC recommended verbal risk descriptors.

Discussion: The current verbal risk descriptors used in PILs are ineffective at best and misleading at worst. Discontinuing the use of verbal risk descriptors would limit the likelihood of people overestimating the risk of side effects.

Potential Teratogenic Effects of Clomiphene Citrate

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ABSTRACT

Clomiphene citrate (CC) is the oldest drug used to regulate the process of ovulation. Considering the great use of CC over the last 40 years, it is important to understand the possible risks associated with its use. The aim of this review was to evaluate the possible teratogenic effects of CC, analyzing results obtained from animal and human studies. The pharmacokinetics of CC and possible mechanisms involved in teratogenesis are examined. Fetal exposure to CC is possible due to the long half-life of CC and its metabolites. Alarming data have emerged from animal studies, although controversial results come from human studies. There is some evidence regarding a possible association of CC exposure and fetal malformations, mainly neural tube defects and hypospadias, which would require further investigation in order to allow safer use of this useful drug.

Second-Generation Antipsychotics and Metabolic Side Effects: A Systematic Review of Population-Based Studies

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ABSTRACT

Introduction: There is strong evidence from randomized controlled trials (RCTs) that second-generation antipsychotic (SGA) medications are associated with metabolic adverse events. However, with the recent increases in the use of SGAs worldwide and frequent off-label use, it is unclear whether these associations are generalizable to populations beyond those included in RCTs.

Objectives: This review aims to characterize the impact of SGAs on the population through a systematic review of population-based studies of SGA users. Studies could examine the use of any SGA medication and any comparator group. Studies also needed to include at least one metabolic outcome such as type 2 diabetes mellitus, dyslipidemia, obesity, hypertension, or metabolic syndrome.

Methods: A systematic search process was used to identify studies for inclusion in this review. Included studies had to be population-based studies of users of any SGA medication with at least one reported metabolic outcome. Study quality was also assessed using the AMSTAR tool, and evidence was synthesized by both metabolic outcome and specific SGA medication.

Results: In total, 15 studies were included in this review. Type 2 diabetes mellitus was the most frequently reported outcome; clozapine and olanzapine were most strongly associated with type 2 diabetes mellitus. Evidence was mixed for a moderate association between type 2 diabetes mellitus and risperidone or quetiapine. Few studies examined other metabolic outcomes, and therefore it is difficult to estimate the true effect in the population.

Discussion: Population-based evidence for other SGAs and metabolic outcomes was limited. However, clozapine and olanzapine were consistently more strongly associated with metabolic adverse events than were other SGAs currently available.

The Incidence of Drug- and Herbal and Dietary Supplement-Induced Liver Injury: Preliminary Findings from Gastroenterologist-Based Surveillance in the Population of the State of Delaware

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ABSTRACT

Background and aim: The population-based incidence rate of drug-induced liver injury (DILI) in the USA is not known. The Drug-Induced Liver Injury Network (DILIN) accrues cases of hepatotoxicity due to medications and herbal and dietary supplements (HDS) from limited geographical areas. The current analysis was an ancillary study of DILIN aimed at determining the annual incidence of DILI in the USA on a population basis, through surveillance in the state of Delaware.

Methods: At the outset of the study, there were 41 gastroenterologists in the state of Delaware and all agreed to participate in surveillance for DILI, which comprised active reporting of suspected cases to the DILIN. The gastroenterologists underwent training in the diagnosis of DILI and were provided with DILIN inclusion criteria. Only cases that met the DILIN laboratory inclusion criteria in 2014 were included in the incidence calculation, and these patients were invited to participate in the DILIN Prospective Study. The number of suspected cases that met inclusion criteria served as the numerator and the 2014 Delaware adult population as the denominator.

Results: During 2014, 23 patients were identified by the surveillance network, 20 of whom met DILIN laboratory inclusion criteria, leading to an incidence of 2.7 cases of DILI per 100,000 adult residents [95% confidence interval (CI) 1.5–3.9 per 100,000]. Fourteen subjects agreed to participate in the DILIN; six declined. Among enrolled cases, the mean age was 51 years, 57% were women, and 71% were white. Eight cases were attributed to antibiotics (36%) and other drugs (21%) and six to HDS (43%). The pattern of injury was hepatocellular in all HDS cases, but only 50% of conventional drug cases ($p = 0.05$), which more commonly presented with eosinophilia ($p = 0.47$) and higher alkaline phosphatase levels ($p = 0.05$). Half of patients were jaundiced, none developed liver failure, and all recovered without the need for transplantation.

Conclusion: Prospective, gastroenterologist-based surveillance for suspected DILI in Delaware yielded an incidence of 2.7 cases per 100,000 adults in 2014; this is the first prospective estimate of DILI for the USA. Because surveillance was limited to subspecialists, the actual incidence of DILI is likely to be higher. These findings provide a benchmark statistic for the epidemiology of DILI in the United States, to be refined with expansion of the surveillance period.

Evaluation of the Case–Crossover (CCO) Study Design for Adverse Drug Event Detection

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ABSTRACT

Introduction: The case–crossover (CCO) design was originally intended to study exposures characterized as intermittent with acute effects. The performance of the CCO design is not well characterized under alternative exposure and outcome relationships.

Objective: The purpose of this study was to evaluate the ability of the CCO to identify simulated treatment effects under different drug exposures and outcomes relationships while varying the duration of the 1:1 matched risk and control windows.

Methods: The simulated data were obtained from the Observational Medical Dataset Simulator, version 2 (OSIM2). The area under the receiver operator characteristic curve (AUC) was calculated to compare CCO performance across outcome types, simulated relative risk (RR), and duration of risk and control windows.

Results: The AUC for acute outcomes was higher for shorter risk and control windows and improved with higher simulated RR. For example, the AUC for the simulated RR of 4 was 0.95 for a 30-day window length and 0.78 for a 360-day window length. The AUC for the accumulative outcomes increased with longer risk and control windows and stronger simulated RR. For example, the AUC for the simulated RR of 4 was 0.85 for a 360-day window length and 0.23 for a 30-day window length. Risk and control window lengths did not appear to sufficiently alter the AUC for insidious onset outcomes.

Conclusions: The CCO performed best for acute-onset outcomes, but may be useful for exploring adverse outcomes with accumulative effects. Careful consideration must be given to the hypothesized drug exposure and outcome distribution because specification of risk and control window duration affects CCO performance.

An Algorithm to Identify Generic Drugs in the FDA Adverse Event Reporting System

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ABSTRACT

Introduction: Although generic drugs constitute approximately 88% of drugs prescribed in the US, there are no reliable methods to identify generic drugs in the US FDA Adverse Event Reporting System (FAERS).

Objective: The aim of this study was to develop an algorithm for identifying generic drugs in the FAERS.

Data Source: We used 1237 adverse event reports for tamsulosin, levothyroxine, and amphetamine/dextroamphetamine from the publicly available FAERS from 2011–2013, and 277 source case narratives obtained from the FDA.

Methods: Two reviewers independently and in duplicate used a three-item algorithm including the following criteria: manufacturer name, New Drug Application (NDA) number/abbreviated NDA (ANDA), and specific use of the term 'generic' or 'brand' to classify the focal drug of each case report as definitely generic (two of three criteria), probably generic (one of three criteria), brand, and cannot be assessed. Inter-rater reliability was estimated using kappa coefficients, and internal consistency was estimated using Cronbach's alpha. We compared the classification of the drugs as generic versus non-generic in publicly available FAERS compared with the original case reports (reference).

Results: The focal drug was classified as generic (definite or probable) in 15.8% (39/234), 9% (67/742), and 16.7% (42/261) of tamsulosin, levothyroxine and amphetamine/dextroamphetamine cases, respectively (overall kappa 0.89, 95% confidence interval 0.85–0.93), while 37% of reports could not be classified due to incomplete information. Among the drugs classified as generics using the publicly available FAERS, we categorized 95.3% as generic drugs using the original case reports. Among those drugs that did not meet the algorithm-based definition of generic in the publicly available data, 20.9% were reclassified as generics using the original case reports.

Conclusions: The algorithm demonstrated high inter-rater reliability with moderate internal consistency for identifying generic drugs in the FAERS, in our sample. Future efforts should focus on improving the reliability and validity of identifying generics through improving the completeness of reporting in the FAERS.

Role of Medicines of Unknown Identity in Adverse Drug Reaction-Related Hospitalizations in Developing Countries: Evidence from a Cross-Sectional Study in a Teaching Hospital in the Lao People's Democratic Republic

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ABSTRACT

Introduction: The health dangers of medicines of unknown identity (MUIs) [loose pharmaceutical units repackaged in individual bags without labelling of their identity] have been suspected in L/MICs. Using visual and analytical tools to identify MUIs, we investigated the frequency of, and factors associated with, adverse drug reaction (ADR)-related hospitalizations in a central hospital in Vientiane Capital, Lao People's Democratic Republic (PDR).

Methods: All unplanned admissions, except for acute trauma and intentional overdose, were prospectively recorded during a 7-week period in 2013, leading to include 453 adults hospitalized for ≥24 h. The patients or their relatives were interviewed to complete the study questionnaire. MUIs suspected of being involved in ADR(s) were identified through comparison of visual characteristics of tablets/capsules with that of reference medicines (photograph tool), and by proton nuclear magnetic resonance and mass spectrometry analyses. Factors associated with ADRs were identified by multivariate logistic regression.

Results: The frequency of hospitalizations related to an ADR was 5.1% (23/453, 95% confidence interval [CI] 3.1–7.1). Forty-eight (12.8%) patients used MUI(s) in the last 2 weeks preceding hospitalization. They were more likely to be hospitalized because of an ADR (adjusted odds ratio 4.5, 95% CI 1.7–11.5) than patients using medicines of known identity. MUIs were mainly involved in bleeding gastroduodenal ulcers. The photograph tool led to the misidentifications because of look-alike pharmaceutical units in the medicines photograph collection.

Conclusion: According to the results of this study, there is a need to ensure appropriate labelling of medicines at dispensing and to provide well-suited tools to identify MUIs in clinical settings to improve drug safety and patients' care in developing countries with limited capacities for drug analysis.

Occurrence of Multiple Sclerosis after Drug Exposure: Insights From Evidence Mapping

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ABSTRACT

Introduction: The role of drugs in the occurrence of multiple sclerosis (MS) is perceived to be insufficiently investigated.

Objective: The aim of this study was to map and assess the evidence on MS occurrence after drug exposure, in order to identify possible signals of causal association.

Methods: A search strategy was performed in MEDLINE and Embase as of July 2016; references consistent with the aim of the study were analysed to extract relevant measures of causal association between drugs and MS. The Newcastle-Ottawa Scale and appropriate guidelines from the International Society for Pharmacoepidemiology (ISPE) and the International Society of Pharmacovigilance (ISoP) were used to assess the quality of included studies.

Results: After screening 832 articles, 58 were selected (of which 14 were found by checking the reference lists of reviews): 30 case reports and case series, 24 longitudinal studies and four randomized controlled trials. Seven longitudinal studies had good (at least 7 out of 9) quality scores, whereas case reports/case series presented several limitations. Half of included articles focused on immunomodulatory drugs (etanercept, infliximab and adalimumab), especially in case reports/series, suggesting an association with MS occurrence. Contraceptives and antibacterials were investigated in some population-based studies, without definite results.

Conclusion: A heterogeneous pharmacological profile of identified classes emerged. Low strength of evidence and conflicting results highlighted the difficulties in addressing the possible contribution of drugs in MS occurrence. Methodological advances are needed, especially to control the confounding role of underlying disease for specific drug classes.

Macrolides, Digoxin Toxicity and the Risk of Sudden Death: A Population-Based Study

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ABSTRACT

Introduction: Digoxin is commonly prescribed to elderly patients with heart failure and atrial fibrillation, and macrolide antibiotics markedly increase the risk of digoxin toxicity.

Objective: The aim was to determine whether, in older patients receiving digoxin, macrolide antibiotics are associated with sudden death.

Methods: We used a population-based, nested, case–control design from January 1, 1994 to December 31, 2012 in a cohort of Ontario residents aged 66 years or older prescribed digoxin. The primary outcome was the risk of sudden death within 14 days of exposure to one of three antibiotics (erythromycin, clarithromycin, or azithromycin), relative to cefuroxime.

Results: Among 39,072 Ontarians who died suddenly while receiving digoxin, 586 died within 14 days of receiving a study antibiotic. Relative to cefuroxime, we found no statistically significant increase in the risk of sudden death following treatment with erythromycin [adjusted odds ratio (aOR) 0.98; 95% confidence interval (CI) 0.65–1.48], clarithromycin (aOR 1.25; 95% CI 0.94–1.65), or azithromycin (aOR 1.07; 95% CI 0.75–1.53).

Conclusion: This finding reinforces the cardiovascular safety of macrolide antibiotics in a high-risk population.

A New Erice Report Considering the Safety of Medicines in the 21st Century

Ivor Ralph Edwards

ABSTRACT

Pharmacovogilance policy, methods and practice require transformation at all levels to create an integrated, comprehensive, continuously improving system, fulfilling the broader remit of overall healthcare vigilance. In pursuit of this vision, energetic measures, including active engagement with patients, are needed to reduce our ignorance about many aspects of patients' experience of medical therapies and their outcomes, including the benefits, but especially the extensive harm known to be caused by medical interventions. More information and communication in this domain will help set more accurate and realistic public expectations about the benefits and harm of therapy. All aspects of medicines development, regulation and use must be characterized by openness, transparency, ethical practice and a primary focus on the benefit and self-determined choices of patients. Notwithstanding, progress has been made in medicines safety information and communication but significant gaps and deficiencies remain. Promotion of the most beneficial use of medicines and the prevention of harm have not advanced sufficiently. This paper is a report from a group of experts, following previous similar decade reviews: the Erice Declaration (1996) and the Erice Manifesto (2006).

Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works

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ABSTRACT

This article provides an overview of the European Union pharmacovigilance system resulting from the rationalisation and strengthening delivered through the implementation of the revised pharmacovigilance legislation. It outlines the system aims, underlying principles, components and drivers for future change. At its core, the Pharmacovigilance Risk Assessment Committee is responsible for assessing all aspects of the risk management of medicinal products, thus ensuring that medicines approved for the European Union market are optimally used by maximising their benefits and minimising risks. The main objectives of the system are to promote and protect public health by supporting the availability of medicines including those that fulfil previously unmet medical needs, and reducing the burden of adverse drug reactions. These are achieved through a proactive, risk proportionate and patient-centred approach, with high levels of transparency and engagement of civil society. In the European Union, pharmacovigilance is now fully integrated into the life cycle of medicinal products, with the planning of pharmacovigilance activities commencing before a medicine is placed on the market, and companies encouraged to start planning very early in development for high-innovation products. After authorisation, information on the safety of medicines continues to be obtained through a variety of sources, including spontaneous reports of adverse drug reactions or monitoring real-world data. Finally, the measurement of the impact of pharmacovigilance activities, auditing and inspections, as well as capacity building ensure that the system undergoes continuous improvement and can always rely on the best methodologies to safeguard public health.

Frequency and Nature of Medication Errors and Adverse Drug Events in Mental Health Hospitals: a Systematic Review

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ABSTRACT

Introduction: Little is known about the frequency and nature of medication errors (MEs) and adverse drug events (ADEs) that occur in mental health hospitals.

Objectives: This systematic review aims to provide an up-to-date and critical appraisal of the epidemiology and nature of MEs and ADEs in this setting.

Method: Ten electronic databases were searched, including MEDLINE, Embase, CINAHL, International Pharmaceutical Abstracts, PsycINFO, Scopus, British Nursing Index, ASSIA, Web of Science, and Cochrane Database of Systematic Reviews (1999 to October 2016). Studies that examined the rate of MEs or ADEs in mental health hospitals were included, and quality appraisal of the included studies was conducted.

Result: In total, 20 studies were identified. The rate of MEs ranged from 10.6 to 17.5 per 1000 patient-days (n = 2) and of ADEs from 10.0 to 42.0 per 1000 patient-days (n = 2) with 13.0–17.3% of ADEs found to be preventable. ADEs were rated as clinically significant (66.0–71.0%), serious (28.0–31.0%), or life threatening (1.4–2.0%). Prescribing errors occurred in 4.5–6.3% of newly written or omitted prescription items (n = 3); dispensing errors occurred in 4.6% of opportunities for error (n = 1) and in 8.8% of patients (n = 1); and medication administration errors occurred in 3.3–48.0% of opportunities for error (n = 5). MEs and ADEs were frequently associated with psychotropics, with atypical antipsychotic drugs commonly involved. Variability in study setting and data collection methods limited direct comparisons between studies.

Conclusion: Medication errors occur frequently in mental health hospitals and are associated with risk of patient harm. Effective interventions are needed to target these events and improve patient safety.

Lipophilic Statins and the Risk of Intracranial Hemorrhage Following Ischemic Stroke: A Population-Based Study

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ABSTRACT

Background: Statins are commonly prescribed for the secondary prevention of ischemic stroke, but there is conflicting evidence as to whether they increase the risk of intracranial hemorrhage. Lipophilic statins cross the blood–brain barrier more freely than hydrophilic statins and may therefore increase the risk of intracranial hemorrhage.

Objective: To determine whether, in older patients following ischemic stroke, receipt of lipophilic statins was associated with differences in the risk of intracranial hemorrhage.

Methods: We conducted a population-based nested case-control study linking multiple healthcare databases between 1 April, 2001 and 31 March, 2015 in Ontario, Canada. Cases were Ontarians aged 66 years or older receiving a statin within 100 days preceding the development of intracranial hemorrhage within 1 year following ischemic stroke. Each case was matched with up to four controls who experienced ischemic stroke not complicated by intracranial hemorrhage but who also received a statin. We classified statins as lipophilic (atorvastatin, simvastatin, lovastatin, fluvastatin, and cerivastatin) or hydrophilic (pravastatin and rosuvastatin) based on their octanol/water partition coefficients. We calculated the odds ratio for the association between intracranial hemorrhage and receipt of lipophilic statins, with hydrophilic statins as the reference group.

Results: We identified 2766 individuals who experienced intracranial hemorrhage during statin therapy after ischemic stroke and 11,060 matched controls. Relative to hydrophilic statins, lipophilic statins were not associated with an increased risk of intracranial hemorrhage (adjusted odds ratio 1.07; 95% confidence interval 0.97–1.19).

Conclusion: Among patients treated with a statin following ischemic stroke, the risk of intracranial hemorrhage is not influenced by statin lipophilicity.

Muscular Adverse Drug Reactions Associated with Proton Pump Inhibitors: A Disproportionality Analysis Using the Italian National Network of Pharmacovigilance Database

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ABSTRACT

Introduction: Proton pump inhibitors (PPIs) have been implicated in the occurrence of moderate to severe myopathies in several case reports.

Aim: This study was performed to assess the reporting risk of muscular adverse drug reactions (ADRs) associated with PPIs in the Italian National Network of Pharmacovigilance database.

Methods: A disproportionality analysis (case/non-case) was performed using spontaneous reports collected in the database between July 1983 and May 2016. Reporting odds ratio (ROR) and 95% confidence intervals (CIs) were calculated as a measure of disproportionality. In a secondary and tertiary analysis, we explored the association of PPIs with muscular ADRs after taking into account the masking effect of statins. Moreover, the possibility of an interaction between PPIs and statins, leading to the occurrence of muscular ADRs, was also tested.

Results: The study was carried out on 274,108 reports. The ROR of muscular ADRs for PPIs, adjusted for age and gender, was 1.484 (95% CI 1.204–1.829; $p < 0.001$), whereas the ROR for rhabdomyolysis was 0.621 (95% CI 0.258–1.499). Similar results were obtained in the secondary analysis. The tertiary analysis, where PPIs were considered regardless of whether their role was suspected or concomitant, showed a potential disproportionate reporting for the combination PPIs–rhabdomyolysis (ROR 1.667, 95% CI 1.173–2.369; $p < 0.01$). The PPIs–statins combination was not associated with an enhanced ROR of muscular ADRs/rhabdomyolysis compared with statins alone.

Conclusions: This explorative study suggests that the class of PPIs could be involved in reports of muscular ADRs, rather than any other ADR, more frequently than any non-statin drug. Our results must be corroborated by further studies.

Patients' Perspectives on Adverse Drug Reaction Reporting in a Developing Country: A Case Study from Ghana

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ABSTRACT

Introduction: Recent efforts to introduce direct patient reporting into pharmacovigilance systems have proved that patient reports contribute significantly to medicine safety, but there is a paucity of information relating to patients' perspectives regarding adverse drug reaction reporting in developing countries.

Objective: The objective of this study was to explore patients' knowledge, attitudes, behaviours and opinions on spontaneous adverse drug reaction reporting in Ghana.

Methods: A cross-sectional study using questionnaires administered through face-to-face interviews was carried out from 25 August, 2016 to 20 September, 2016 with 442 patients aged 18 years and above selected by convenience sampling from two community pharmacies in urban and rural Ghana. Reasons and opinions on patients' reporting on adverse drug reactions were surveyed using a 5-point Likert scale. The Pearson chi-square test was used to determine associations between background variables and responses on knowledge of adverse drug reaction reporting.

Results: Responses from 434 patients (86.7%) were included in the analysis. Among those interviewed, there was a high level of awareness regarding the existence of the National Pharmacovigilance Centre (81.6%). Approximately half of the respondents (49.5%) were aware that patients were able to report adverse drug reactions associated with medicinal products directly to the National Pharmacovigilance Centre. Of the respondents, 46.3% stated that they had an adverse drug reaction to their medicines in the past; of these, 53.2% reported to healthcare professionals and 36.9% failed to report because they stopped their medication. The three main reasons for patients' reporting were desire for extra information (92.4%), desire to share experiences with other people (91.7%) and expectation for the National Pharmacovigilance Centre to inform others about the possible adverse drug reactions (88.0%). Patients' opinions were to contribute to research/knowledge (96.5%) and improvements in drug safety (96.5%). Patients' behaviour towards adverse drug reaction reporting was affected by the likely consequences of reporting, influence of others and the ease of reporting.

Conclusion: Patients have a positive attitude and good knowledge on adverse drug reaction reporting to the National Pharmacovigilance Centre and report because they expect extra information and to contribute to drug safety. Patients' positive attitude towards adverse drug reaction reporting could be sustained by hosting periodic public awareness campaigns addressing the importance of adverse drug reaction reporting and by providing timely feedback to patients on regulatory decisions taken as a result of the reports that they submitted.

Updating the Evidence of the Interaction between Clopidogrel and CYP2C19-Inhibiting Selective Serotonin Reuptake Inhibitors: A Cohort Study and Meta-Analysis

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ABSTRACT

Introduction: We previously found that patients who initiate clopidogrel while treated with a cytochrome P450 (CYP) 2C19-inhibiting selective serotonin reuptake inhibitor (SSRI) have a higher risk of subsequent ischemic events than patients treated with other SSRIs. It is not known whether initiating an inhibiting SSRI while treated with clopidogrel will also increase risk of ischemic events.

Objective: The aim of this study was to assess clinical outcomes following initiation of a CYP2C19-inhibiting SSRI versus initiation of other SSRIs among patients treated with clopidogrel and to update existing evidence on the clinical impact of clopidogrel–SSRI interaction.

Methods: Using five US databases (1998–2013), we conducted a cohort study of clopidogrel initiators who encountered treatment with SSRI during their clopidogrel therapy. Patients were matched by propensity score (PS) and followed for as long as they were exposed to both clopidogrel and index SSRI group. Outcomes were a composite ischemic event (myocardial infarction, ischemic stroke, or a revascularization procedure, whichever came first) and a composite major bleeding event (gastrointestinal bleed or hemorrhagic stroke, whichever came first). Results were combined via random-effects meta-analysis with previous evidence from subjects initiating clopidogrel while on SSRI therapy.

Results: The PS-matched cohort comprised 2346 clopidogrel users starting CYP2C19-inhibiting SSRI therapy and 16,115 starting other SSRIs (mean age 61 years; 59% female). Compared with those treated with a non-inhibiting SSRI, the hazard ratio (HR) for patients treated with a CYP2C19-inhibiting SSRI was 1.07 (95% confidence interval [CI] 0.82–1.40) for the ischemic outcome and 1.00 (95% CI 0.42–2.36) for bleeding. The pooled estimates were 1.11 (95% CI 1.01–1.22) for ischemic events and 0.80 (95% CI 0.55–1.18) for bleeding.

Conclusions: We observed similar estimates of association between the two studies. The updated evidence still indicates a small decrease in clopidogrel effectiveness associated with concomitant exposure to clopidogrel and CYP2C19-inhibiting SSRIs.

Clinical Relevance and Predictive Value of Damage Biomarkers of Drug-Induced Kidney Injury

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ABSTRACT

Nephrotoxin exposure accounts for up to one-fourth of acute kidney injury episodes in hospitalized patients, and the associated consequences are as severe as acute kidney injury due to other etiologies. As the use of nephrotoxic agents represents one of the few modifiable risk factors for acute kidney injury, clinicians must be able to identify patients at high risk for drug-induced kidney injury rapidly. Recently, significant advancements have been made in the field of biomarker utilization for the prediction and detection of acute kidney injury. Such biomarkers may have a role both for detection of drug-induced kidney disease and implementation of preventative and therapeutic strategies designed to mitigate injury. In this article, basic principles of renal biomarker use in practice are summarized, and the existing evidence for six markers specifically used to detect drug-induced kidney injury are outlined, including liver-type fatty acid binding protein, neutrophil gelatinase-associated lipocalin, tissue inhibitor of metalloproteinase-2 times insulin-like growth factor-binding protein 7 ([TIMP-2]·[IGFBP7]), kidney injury molecule-1 and N-acetyl-β-d-glucosaminidase. The results of the literature search for these six kidney damage biomarkers identified 29 unique articles with none detected for liver-type fatty acid binding protein and [TIMP-2]·[IGFBP7]. For three biomarkers, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin and N-acetyl-β-d-glucosaminidase, the majority of the studies suggest utility in clinical practice. While many questions need to be answered to clearly articulate the use of biomarkers to predict drug-induced kidney disease, current data are promising.

Natural Language Processing for EHR-Based Pharmacovigilance: A Structured Review

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ABSTRACT

The goal of pharmacovigilance is to detect, monitor, characterize and prevent adverse drug events (ADEs) with pharmaceutical products. This article is a comprehensive structured review of recent advances in applying natural language processing (NLP) to electronic health record (EHR) narratives for pharmacovigilance. We review methods of varying complexity and problem focus, summarize the current state-of-the-art in methodology advancement, discuss limitations and point out several promising future directions. The ability to accurately capture both semantic and syntactic structures in clinical narratives becomes increasingly critical to enable efficient and accurate ADE detection. Significant progress has been made in algorithm development and resource construction since 2000. Since 2012, statistical analysis and machine learning methods have gained traction in automation of ADE mining from EHR narratives. Current state-of-the-art methods for NLP-based ADE detection from EHRs show promise regarding their integration into production pharmacovigilance systems. In addition, integrating multifaceted, heterogeneous data sources has shown promise in improving ADE detection and has become increasingly adopted. On the other hand, challenges and opportunities remain across the frontier of NLP application to EHR-based pharmacovigilance, including proper characterization of ADE context, differentiation between off- and on-label drug-use ADEs, recognition of the importance of polypharmacy-induced ADEs, better integration of heterogeneous data sources, creation of shared corpora, and organization of shared-task challenges to advance the state-of-the-art.

Safety and Interactions of Direct Oral Anticoagulants with Antiarrhythmic Drugs

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ABSTRACT

Direct oral anticoagulants (DOACs) are novel direct-acting medications that are selective for either thrombin or activated factor X. Due to their obvious benefits for patients (fewer interactions, broader therapeutic window, etc.), they are increasingly used as an alternative to warfarin, phenprocoumon, or acenocoumarol. One of the major indications for use of DOACs is stroke prevention in patients with atrial fibrillation (AF). However, interactions still exist, especially in combination with antiarrhythmic drugs (AADs), which are frequently given to AF patients for rhythm or rate control. These interactions are due to the cytochrome P450 system and the P-glycoprotein (permeability glycoprotein or multidrug resistance protein) transport system. For some combinations, dose reduction of the DOAC is recommended and in some cases contraindications exist. In addition, impairment in renal and hepatic function plays an important role in this context. However, compared with pure interactions where data are quite convincing, the latter topic has been studied only rudimentarily. This review summarizes the literature on the safety and interactions of AADs when used with DOACs [dabigatran (a direct inhibitor of factor IIa) and rivaroxaban, apixaban and edoxaban (direct inhibitors of factor Xa)] and the impact of renal and hepatic impairment.

Impact of Medicine Withdrawal on Reporting of Adverse Events Involving Therapeutic Alternatives: A Study from the French Spontaneous Reporting Database

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ABSTRACT

Introduction: The consequences of the withdrawal of marketing authorisation of drugs have mostly been studied considering drug prescription patterns for the therapeutic alternatives of the withdrawn drugs. The potential concomitant changes in the reporting of adverse reactions concerning these alternatives have been studied less often.

Objective: The objective of this study was to analyse the changes in the reporting of adverse events (AEs) for therapeutic alternatives after the withdrawal of three medicines (dextropropoxyphene, pioglitazone and tetrazepam) from the market for safety reasons.

Methods: This study was performed using both the French pharmacovigilance database and the Echantillon Généraliste des Bénéficiaires (a random sample of French health insurance affiliates). For dextropropoxyphene, pioglitazone and tetrazepam alternatives, the number and types of case reports were studied for both the year preceding the first official safety warning and the year following the withdrawal. Reporting rates expressed per 10,000 reimbursements (RRReimb) and per 10,000 treated patients (RRPat) were also compared for the two periods.

Results: After dextropropoxyphene withdrawal, case reports and reimbursements increased for tramadol (case reports: +23%, reimbursements: +13%) and codeine (case reports: +74%, reimbursements: +47%), RRPat being significantly increased for tramadol (0.92 vs. 1.06, p = 0.02). After pioglitazone withdrawal, case reports increased for dipeptidyl peptidase-4 (DPP-4) inhibitors, glinides, and glucagon-like peptide 1 (GLP-1) analogues (+84%, +22% and +5%, respectively) and reimbursements (+55, +11 and +50%, respectively); both decreased for sulfonylureas (case reports: −6%, reimbursements: −2%). RRPat increased for DPP-4 inhibitors (1.63 vs. 2.26, p = 0.008). After tetrazepam withdrawal, case reports increased for diazepam, methocarbamol and thiocolchicoside (+110, +86 and +157%, respectively), as lesser did reimbursements. RRPat increased for diazepam (1.78 vs. 2.41, p = 0.054) and thiocolchicoside (0.14 vs. 0.24, p = 0.013).

Conclusion: For the three drug withdrawals investigated, the number of case reports involving alternatives increased to a larger extent than the numbers of prescriptions. This could relate to a higher occurrence of AEs in new users of alternatives who switched from the withdrawn medicines or to an increased awareness of possible AEs.

Association of Parkinsonism or Parkinson Disease with Polypharmacy in the Year Preceding Diagnosis: A Nested Case–Control Study in South Korea

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ABSTRACT

Introduction: Published studies on the association between polypharmacy and parkinsonism or Parkinson disease are very limited.

Objective: The objective of this study was to investigate whether polypharmacy is associated with parkinsonism or Parkinson disease in elderly patients.

Methods: From a South Korean national health insurance sample cohort database for 2002–2013, we matched parkinsonism cases (defined by diagnosis codes for parkinsonism/Parkinson disease) and Parkinson disease cases (patients who had records for both Parkinson disease diagnosis and anti-Parkinson disease drug prescriptions) with controls. Logistic regression analysis evaluated the associations of parkinsonism/Parkinson disease with polypharmacy (i.e., five or more prescribed daily drugs) during the year preceding parkinsonism/Parkinson disease diagnosis, medications potentially associated with parkinsonism, and comorbidity status (using the Charlson Comorbidity Index score and hospitalization records).

Results: The study population included 6209 cases and 24,836 controls for parkinsonism and 1331 cases and 5324 controls for Parkinson disease. In univariate logistic regression, odds ratios for parkinsonism/Parkinson disease increased significantly with increased polypharmacy, medications potentially associated with parkinsonism, Charlson Comorbidity Index score, or prior hospitalizations. In multiple logistic regression, odds ratios for parkinsonism/Parkinson disease (adjusted for medications potentially associated with parkinsonism and comorbidities) also increased with increased polypharmacy. Odds ratios (95% confidence interval) for Parkinson disease were higher than those for parkinsonism with stronger statistical significance: 1.41 (1.28–1.55) and 2.17 (1.84–2.57) for parkinsonism and 2.87 (2.30–3.58) and 4.75 (3.39–6.66) for Parkinson disease for between five and ten prescribed daily drugs and ten or more drugs, respectively.

Conclusions: Polypharmacy in the year preceding diagnosis may be associated with an increased risk for parkinsonism/Parkinson disease. Medications potentially associated with parkinsonism were assumed to increase the risk for parkinsonism/Parkinson disease, but more studies are required to confirm this relationship.

Using Multiple Pharmacovigilance Models Improves the Timeliness of Signal Detection in Simulated Prospective Surveillance

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ABSTRACT

Introduction: Prospective pharmacovigilance aims to rapidly detect safety concerns related to medical products. The exposure model selected for pharmacovigilance impacts the timeliness of signal detection. However, in most real-life pharmacovigilance studies, little is known about which model correctly represents the association and there is no evidence to guide the selection of an exposure model. Different exposure models reflect different aspects of exposure history, and their relevance varies across studies. Therefore, one potential solution is to apply several alternative exposure models simultaneously, with each model assuming a different exposure–risk association, and then combine the model results.

Methods: We simulated alternative clinically plausible associations between time-varying drug exposure and the hazard of an adverse event. Prospective surveillance was conducted on the simulated data by estimating parametric and semi-parametric exposure–risk models at multiple times during follow-up. For each model separately, and using combined evidence from different subsets of models, we compared the time to signal detection.

Results: Timely detection across the simulated associations was obtained by fitting a set of pharmacovigilance models. This set included alternative parametric models that assumed different exposure–risk associations and flexible models that made no assumptions regarding the form/shape of the association. Times to detection generated using a simple combination of evidence from multiple models were comparable to those observed under the ideal, but unrealistic, scenario where pharmacovigilance relied on the single ‘true’ model used for data generation.

Conclusions: Simulation results indicate that, if the true model is not known, an association can be detected in a more timely manner by first fitting a carefully selected set of exposure–risk models and then generating a signal as soon as any of the models considered yields a test statistic value below a predetermined testing threshold.

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

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ABSTRACT

Introduction: Anti-vascular endothelial growth factor (anti-VEGF) drugs are widely used for the treatment of several cancers and retinal diseases. The systemic use of anti-VEGF drugs has been associated with an increased risk of serious adverse reactions. Whether this risk is also related to intravitreal administration of anti-VEGF drugs is unclear.

Objective: The aim of this study was to provide an overview of the safety of anti-VEGF drugs in oncology and ophthalmology settings using the Italian Spontaneous Reporting System (SRS).

Methods: We selected all suspected adverse drug reaction (ADR) reports attributed to anti-VEGF drugs and conducted descriptive frequency analyses stratified by indication of use. As a measure of disproportionality, we calculated the proportional reporting ratio with 95% confidence intervals at the level of standardized Medical Dictionary for Regulatory Activities (MedDRA®) queries (SMQs).

Results: Of a total of 2472 anti-VEGF drug-related reports, 2173 (87.9%) and 299 (12.1%) were attributed to systemic and intravitreal use of these drugs, respectively. The frequency of serious ADRs reported was higher for intravitreal administration of anti-VEGF drugs than for systemic use in patients with cancer (58.9 vs. 34.1%) ($p < 0.001$) and were disproportionally associated with ischemic heart disease and thromboembolic and cerebrovascular events. Most serious ADRs related to anti-VEGF drugs in patients with cancer are known and clinically relevant (e.g., gastrointestinal and vascular disorders).

Conclusions: This study documented that serious ADRs and systemic toxicity may occur not only with systemic use of anti-VEGF drugs in patients with cancer but also with intravitreal administration. Close monitoring of cardio/cerebrovascular adverse events should be considered during treatment with all anti-VEGF drugs.

Signal of Miscarriage with Aripiprazole: A Disproportionality Analysis of the Japanese Adverse Drug Event Report Database

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ABSTRACT

Introduction: With recent advances in medicines, many patients with schizophrenia have become able to conceive. One common second-generation antipsychotic given to patients with schizophrenia is aripiprazole. The label information of aripiprazole in Japan states that according to one case report "there is a report of miscarriage in clinical trial".

Objective: The aim of this study was to evaluate the relationship between aripiprazole and miscarriage by conducting a disproportionality analysis of an adverse drug event report database.

Methods: We conducted a disproportionality analysis of second-generation antipsychotic exposure during pregnancy using the Japanese Adverse Drug Event Report database, which is a spontaneous reporting database in Japan. We investigated aripiprazole and other approved second-generation antipsychotics in Japan. In accordance with the previous report, we created a data set for analysis consisting of pregnancy-related reports.

Results: A potential signal for miscarriage was detected for aripiprazole [proportional reporting ratio: 2.39, $\chi 2$: 13.77, reporting odds ratio (95% confidence interval): 2.76 (1.62–4.69); n = 18]. In contrast, no potential signal for miscarriage was detected for other second-generation antipsychotics.

Conclusion: Through our analysis of the Japanese Adverse Drug Event Report database, we found a potential signal for miscarriage for aripiprazole. Safety information on the use of aripiprazole during pregnancy is very limited. Therefore, we suggest that the potential signal detected in our analysis be explored further.

The Fetal Safety of Enoxaparin Use during Pregnancy: A Population-Based Retrospective Cohort Study

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ABSTRACT

Introduction: Enoxaparin is widely used during pregnancy as pregnancy is a hypercoagulable state; however, its fetal safety has scarcely been investigated.

Objective: Our study aimed to examine fetal safety following enoxaparin exposure during pregnancy.

Methods: A population-based, retrospective cohort study was performed by linking computerized databases, including the drug dispensing registries of Clalit Health Services in Israel and maternal and infant hospital records, between 1998 and 2009. Multivariate logistic regression models were used to examine associations between first- and third-trimester exposure to enoxaparin, major malformations, and other adverse birth outcomes, adjusted for confounders.

Results: From a total of 109,473 singleton pregnancies, 418 and 572 were exposed to enoxaparin during the first and third trimesters, respectively. Exposure to enoxaparin during the first trimester of pregnancy was not associated with an increased risk of major congenital malformations [adjusted odds ratio (aOR) 1.1, 95% confidence interval (CI) 0.8–1.6], while exposure during the third trimester was not associated with an increased risk of low birth weight (aOR 1.1, 95% CI 0.8–1.4), low Apgar score (aOR 0.9, 95% CI 0.4–1.8), or risk of perinatal mortality (aOR 0.6, 95% CI 0.1–2.9).

Conclusion: Exposure to enoxaparin during pregnancy was not associated with an increased risk of major malformations in general or according to organ systems. Nonetheless, risk for specific malformations cannot be ruled out.

Neurological Adverse Effects Attributable to β-Lactam Antibiotics: A Literature

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ABSTRACT

β-lactam antibiotics are commonly prescribed antibiotic drugs. To describe the clinical characteristics, risk markers and outcomes of β-lactam antibiotic-induced neurological adverse effects, we performed a general literature review to provide updated clinical data about the most used β-lactam antibiotics. For selected drugs in each class available in France (ticarcillin, piperacillin, temocillin, ceftazidime, cefepime, cefpirome, ceftaroline, ceftobiprole, ceftolozane, ertapenem and aztreonam), a systematic literature review was performed up to April 2016 via an electronic search on PubMed. Articles that reported original data, written in French, Spanish, Portuguese or English, with available individual data for patients with neurological symptoms (such as seizure, disturbed vigilance, confusional state, myoclonia, localising signs, and/or hallucinations) after the introduction of a β-lactam antibiotic were included. The neurological adverse effects of piperacillin and ertapenem are often described as seizures and hallucinations (>50 and 25% of cases, respectively). Antibiotic treatment is often adapted to renal function (>70%), and underlying brain abnormalities are seen in one in four to one in three cases. By contrast, the neurological adverse drug reactions of ceftazidime and cefepime often include abnormal movements but few hallucinations and seizures. These reactions are associated with renal insufficiency (>80%) and doses are rarely adapted to renal function. Otherwise, it appears that monobactams do not have serious neurological adverse drug reactions and that valproic acid and carbapenem combinations should be avoided. The onset of disturbed vigilance, myoclonus, and/or seizure in a patient taking β-lactam antibiotics, especially if associated with renal insufficiency or underlying brain abnormalities, should lead physicians to suspect adverse drug reactions and to consider changes in antibacterial therapy.

Commercial Online Social Network Data and Statin Side-Effect Surveillance: A Pilot Observational Study of Aggregate Mentions on Facebook

Marco D. Huesch

ABSTRACT

Introduction: Surveillance of the safety of prescribed drugs after marketing approval has been secured remains fraught with complications. Formal ascertainment by providers and reporting to adverse-event registries, formal surveys by manufacturers, and mining of electronic medical records are all well-known approaches with varying degrees of difficulty, cost, and success. Novel approaches may be a useful adjunct, especially approaches that mine or sample internet-based methods such as online social networks.

Methods: A novel commercial software-as-a-service data-mining product supplied by Sysomos from Datasift/Facebook was used to mine all mentions on Facebook of statins and stain-related side effects in the US in the 1-month period 9 January 2017 through 8 February 2017.

Results: A total of 4.3% of all 25,700 mentions of statins also mentioned typical stain-related side effects. Multiple methodological weaknesses stymie interpretation of this percentage, which is however not inconsistent with estimates that 5–20% of patients taking statins will experience typical side effects at some time.

Conclusions: Future work on pharmacovigilance may be informed by this novel commercial tool, but the inability to mine the full text of a posting poses serious challenges to content categorization.

The Ribavirin Pregnancy Registry: An Interim Analysis of Potential Teratogenicity at the Mid-Point of Enrollment

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ABSTRACT

Introduction: Significant teratogenic effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin is prescribed for chronic hepatitis C and is contraindicated in women who are pregnant and in the male sexual partners of women who are pregnant. Both sexes are advised to avoid pregnancy for 6 months after exposure. The Ribavirin Pregnancy Registry was established in 2003 to monitor pregnancy exposures to ribavirin for signals of possible human teratogenicity.

Methods: This voluntary registry enrolls pregnant women with prenatal exposure to ribavirin. Exposure is classified as direct—women taking ribavirin during pregnancy or the 6 months prior to conception—or indirect—women exposed through sexual contact, 6 months prior to or during pregnancy, with a man who is taking or has taken ribavirin in the past 6 months. Women are followed until delivery and infants for 1 year. When enrollment is complete, birth defect rates will be compared with the Metropolitan Atlanta Congenital Defects Program's published rate of 2.67. Using data collected since inception in 2003 through February 2016, preliminary rates were calculated.

Results: The registry has enrolled 272 pregnant women, with 180 live births: there were seven birth defect cases among 85 directly exposed women [7/85 (8.2%) (95% confidence interval (CI) 3.4–16.2)] and four birth defect cases among 95 indirectly exposed women [4/95 (4.2%) (95% CI 1.2–10.4)]. Of the 11 infants, nine had structural defects and two had chromosomal anomalies. Patterns suggesting a common etiology or relationship with ribavirin exposure are not seen.

Conclusion: Based on the patterns of birth defects reported, preliminary findings do not suggest a clear signal of human teratogenicity for ribavirin. However, the current sample size is insufficient for definitive conclusions, and ribavirin exposure should be avoided during pregnancy and during the 6 months prior to pregnancy, in accordance with prescribing information.

Suspected Adverse Effects after Human Papillomavirus Vaccination: A Temporal Relationship between Vaccine Administration and the Appearance of Symptoms in Japan

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ABSTRACT

Introduction: In Japan, after receiving human papillomavirus vaccination, a significant number of adolescent girls experienced various symptoms, the vast majority of which have been ascribed to chronic regional pain syndrome, orthostatic intolerance, and/or cognitive dysfunction. However, a causal link has not been established between human papillomavirus vaccination and the development of these symptoms.

Objective: The aim of this study was to clarify the temporal relationship between human papillomavirus vaccination and the appearance of post-vaccination symptoms.

Methods: Between June 2013 and December 2016, we examined symptoms and objective findings in 163 female patients who had received human papillomavirus vaccination. We used newly defined diagnostic criteria for accurate inclusion of patients who experienced adverse symptoms after human papillomavirus vaccination; these diagnostic criteria were created for this study, and thus their validity and reliability have not been established.

Results: Overall, 43 female patients were excluded. Among the remaining 120 patients, 30 were diagnosed as having definite vaccine-related symptoms, and 42 were diagnosed as probable. Among these 72 patients, the age at initial vaccination ranged from 11 to 19 years (average 13.6 ± 1.6 years), and the age at appearance of symptoms ranged from 12 to 20 years (average 14.4 ± 1.7 years). The patients received the initial human papillomavirus vaccine injection between May 2010 and April 2013. The first affected girl developed symptoms in October 2010, and the last two affected girls developed symptoms in October 2015. The time to onset after the first vaccine dose ranged from 1 to 1532 days (average 319.7 ± 349.3 days).

Conclusions: The period of human papillomavirus vaccination considerably overlapped with that of unique post-vaccination symptom development. Based on these sequential events, it is suggested that human papillomavirus vaccination is related to the transiently high prevalence of the previously mentioned symptoms including chronic regional pain syndrome and autonomic and cognitive dysfunctions in the vaccinated patients.

Safety Profile of Eslicarbazepine Acetate as Add-On Therapy in Adults with Refractory Focal-Onset Seizures: From Clinical Studies to 6 Years of Post-Marketing Experience

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ABSTRACT

Introduction: Eslicarbazepine acetate was first approved in the European Union in 2009 as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization.

Objective: The objective of this study was to review the safety profile of eslicarbazepine acetate analyzing the data from several clinical studies to 6 years of post-marketing surveillance.

Methods: We used a post-hoc pooled safety analysis of four phase III, double-blind, randomized, placebo-controlled studies (BIA-2093-301, -302, -303, -304) of eslicarbazepine acetate as add-on therapy in adults. Safety data of eslicarbazepine acetate in special populations of patients aged ≥65 years with partial-onset seizures (BIA-2093-401) and subjects with moderate hepatic impairment (BIA-2093-111) and renal impairment (BIA-2093-112) are also considered. The incidences of treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation, and serious adverse events were analyzed. The global safety database of eslicarbazepine acetate was analyzed for all cases from post-marketing surveillance from 1 October, 2009 to 21 October, 2015.

Results: From a pooled analysis of four phase III studies, it was concluded that the incidence of treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation, and adverse drug reactions were dose dependent. Dizziness, somnolence, headache, and nausea were the most common treatment-emergent adverse events (≥10% of patients) and the majority were of mild-to-moderate intensity. No dose-dependent trend was observed for serious adverse events and individual serious adverse events were reported in less than 1% of patients. Hyponatremia was classified as a possibly related treatment-emergent adverse event in phase III studies (1.2%); however, after 6 years of post-marketing surveillance it represents the most frequently (10.2%) reported adverse drug reaction, with more than half of these cases occurring with eslicarbazepine acetate at daily doses of 1200 mg. Other adverse drug reactions reported in post-marketing surveillance are seizure (5.8%), dizziness (4.1%), rash (2.6%), and fatigue (2.1%). The safety profile of eslicarbazepine acetate in renal and hepatic impairment subjects (phase I studies) and in elderly patients (phase III study) did not raise any specific concern.

Conclusion: After 6 years of post-marketing surveillance, eslicarbazepine acetate maintains a similar safety profile to that observed in pivotal clinical studies.

Medication Errors: A Characterisation of Spontaneously Reported Cases in EudraVigilance

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ABSTRACT

Introduction: Medication errors recently became the focus of regulatory guidance in pharmacovigilance to support reporting, evaluation and prevention of medication errors.

Objective: This study aims to characterise spontaneously reported cases of medication errors in EudraVigilance over the period 2002–2015 before the release of EU good practice guidance.

Methods: Case reports were identified through the adverse reaction section where a Medical Dictionary for Regulatory Activities (MedDRA®) term is reported and included in the Standardised MedDRA® Query (SMQ) for medication errors. These case reports were further categorised by MedDRA® terms, geographical region, patient age group and Anatomical Therapeutic Chemical classification system of suspect medicinal product(s).

Results: A total of 147,824 case reports were retrieved, 41,355 of which were from the European Economic Area (EEA). Approximately 60% of these case reports were retrieved with the narrow SMQ. The absolute number of medication error case reports and the proportion to the total number of reports in EudraVigilance increased during the study period, with peaks seen around 2005 and 2012 for cases with EEA origin. Fifty-two percent of case reports in which age was provided occurred in adults, 30% in the elderly and 18% in children, with almost half of these in children aged 2 months to 2 years.

Conclusion: Case reports of medication errors in EudraVigilance steadily increased between 2005 and 2015, the reasons for which may be multifactorial, including increased awareness, changes to the MedDRA® terminology and the 2012 EU pharmacovigilance legislation and associated guidance for stakeholders, or a generally increased risk for errors as more medications become available.

Drug-Induced Dental Caries: A Disproportionality Analysis Using Data from VigiBase

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ABSTRACT

Introduction: Dental caries is defined as a pathological breakdown of the tooth. It is an infectious phenomenon involving a multifactorial aetiology. The impact of drugs on cariogenic risk has been poorly investigated.

Objectives: In this study, we identified drugs suspected to induce dental caries as adverse drug reactions (ADRs) and then studied a possible pathogenic mechanism for each drug that had a statistically significant disproportionality.

Methods: We extracted individual case safety reports of dental caries associated with drugs from VigiBase® (the World Health Organization global individual case safety report database). We calculated disproportionality for each drug with a reporting odds ratio (ROR) and 99% confidence interval. We analysed the pharmacodynamics of each drug that had a statistically significant disproportionality.

Results: In VigiBase®, 5229 safety reports for dental caries concerning 733 drugs were identified. Among these drugs, 88 had a significant ROR, and for 65 of them (73.9%), no information about dental caries was found in the summaries of the product characteristics, the Micromedex® DRUGDEX, or the Martindale databases. Regarding the pharmacological classes of drugs involved in dental caries, we identified bisphosphonates, atropinic drugs, antidepressants, corticoids, immunomodulating drugs, antipsychotics, antiepileptics, opioids and β2-adrenoreceptor agonist drugs. Regarding possible pathogenic mechanisms for these drugs, we identified changes in salivary flow/composition for 54 drugs (61.4%), bone metabolism changes for 31 drugs (35.2%), hyperglycaemia for 32 drugs (36.4%) and/or immunosuppression for 23 drugs (26.1%). For nine drugs (10.2%), the mechanism was unclear.

Conclusion: We identified 88 drugs with a significant positive disproportionality for dental caries. Special attention has to be paid to bisphosphonates, atropinic drugs, immunosuppressants and drugs causing hyperglycaemia.

A Pharmacoepidemiology Database System for Monitoring Risk Due to the Use of Medicines by New Zealand Primary Care Patients

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ABSTRACT

Introduction: The use of large record-linked healthcare databases for drug safety research and surveillance is now accepted practice. New Zealand's standardized national healthcare datasets provide the potential to automate the conduct of pharmacoepidemiological studies to provide rapid validation of medicine safety signals.

Objectives: Our objectives were to describe the methodology undertaken by a semi-automated computer system developed to rapidly assess risk due to drug exposure in New Zealand's population of primary care patients and to compare results from three studies with previously published findings.

Methods: Data from three national databases were linked at the patient level in the automated studies. A retrospective nested case–control design was used to evaluate risk for upper gastrointestinal bleeding (UGIB), acute kidney failure (AKF), and serious arrhythmia associated with individual medicines, therapeutic classes of medicines, and concurrent use of medicines from multiple therapeutic classes.

Results: The patient cohort available for each study included 5,194,256 patients registered between 2007 and 2014, with a total of 34,630,673 patient-years at risk. An increased risk for UGIB was associated with non-steroidal anti-inflammatory drugs (NSAIDs) (adjusted odds ratio [AOR] 4.16, 95% confidence interval [CI] 3.90–4.43, $p < 0.001$) and selective serotonin reuptake inhibitors (AOR 1.39, 95% CI 1.20–1.62, $p < 0.001$); an increased risk for AKF was associated with NSAIDs (AOR 1.78, 95% CI 1.73–1.83, $p < 0.001$) and proton pump inhibitors (AOR 1.78, 95% CI 1.72–1.83, $p < 0.001$); and an increased risk for serious arrhythmia was associated with fluoroquinolones (AOR 1.38, 95% CI 1.26–151, $p < 0.001$) and penicillins (AOR 1.69, 95% CI 1.61–1.77, $p < 0.001$).

Conclusions: Automated case–control studies using New Zealand's healthcare datasets can replicate associations of risk with drug exposure consistent with previous findings. Their speed of conduct enables systematic monitoring of risk for adverse events associated with a wide range of medicines.

Channeling in the Use of Nonprescription Paracetamol and Ibuprofen in an Electronic Medical Records Database: Evidence and Implications

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ABSTRACT

Introduction: Over-the-counter analgesics such as paracetamol and ibuprofen are among the most widely used, and having a good understanding of their safety profile is important to public health. Prior observational studies estimating the risks associated with paracetamol use acknowledge the inherent limitations of these studies. One threat to the validity of observational studies is channeling bias, i.e. the notion that patients are systematically exposed to one drug or the other, based on current and past comorbidities, in a manner that affects estimated relative risk.

Objectives: The aim of this study was to examine whether evidence of channeling bias exists in observational studies that compare paracetamol with ibuprofen, and, if so, the extent to which confounding adjustment can mitigate this bias.

Study Design and Setting: In a cohort of 140,770 patients, we examined whether those who received any paracetamol (including concomitant users) were more likely to have prior diagnoses of gastrointestinal (GI) bleeding, myocardial infarction (MI), stroke, or renal disease than those who received ibuprofen alone. We compared propensity score distributions between drugs, and examined the degree to which channeling bias could be controlled using a combination of negative control disease outcome models and large-scale propensity score matching. Analyses were conducted using the Clinical Practice Research Datalink.

Results: The proportions of prior MI, GI bleeding, renal disease, and stroke were significantly higher in those prescribed any paracetamol versus ibuprofen alone, after adjusting for sex and age. We were not able to adequately remove selection bias using a selected set of covariates for propensity score adjustment; however, when we fit the propensity score model using a substantially larger number of covariates, evidence of residual bias was attenuated.

Conclusions: Although using selected covariates for propensity score adjustment may not sufficiently reduce bias, large-scale propensity score matching offers a novel approach to consider mitigating the effects of channeling bias.

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